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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification:

C07H 21/02, 21/04, C12P 19/34, C12Q 1/68

A1

(11) International Publication Number:

WO 95/21853

(43) International Publication Date: 17 August 1995 (17.08.95)

(21) International Application Number: PCT/US93/01458

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(22) International Filing Date: 6 February 1995 (06.02.95)

(30) Priority Date: 10 February 1994 (10.02.94) US 08/193,003

US 08/219,012 28 March 1994 (28.03.94) US

(60) Parent Applications or Claims

(63) Related by Continuation

US 08/193,003 (C27)

Filed on 10 February 1994 (10.02.94)

US 08/219,012 (C27)

Filed on 28 March 1994 (28.03.94)

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(64) Title: HIGH-ABRINTY LIQUIDS OF BASIC FIBROBLAST GROWTH FACTOR AND THROMBIN

(67) Abstract

The present invention utilizes the STELEX (Systematic Evolution of Ligands for Identifying and Preparing Nucleic Acid Ligands) to basic fibroblast growth factor (bFGF) and thrombin. Included in the present invention are nucleic acid ligands to bFGF which are inhibitors of bFGF and 2'-amino-modified RNA ligands to bFGF. Further included in the present invention are modified nucleic acid sequences to thrombin based on the sequence of the RNA ligand identified. The modified RNA ligands to bFGF and thrombin exhibit increased in vivo stability.

Published
With international search report.

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HIGH-AFFINITY LIGANDS OF BASIC FIBROBLAST GROWTH FACTOR AND THROMBIN

FIELD OF THE INVENTION

Described herein are methods for identifying and preparing high-affinity nucleic acid ligands to basic fibroblast growth factor (bFGF) and thrombin. The method utilized herein for identifying such ligands is called SELEX, an acronym for Systematic Evolution of Ligands by EXponential Enrichment. Included within the scope of this invention are the specific ligands identified pursuant to such methods. Specifically, nucleic acid ligands are described to bFGF and thrombin. Also, included within the scope of this invention are modified nucleic acid ligands to bFGF and thrombin. Further included are mimetic nucleic acid ligands that are informed by the nucleic acid ligands identified herein. Specifically, disclosed are 2'-amino (2'-NH₂) modified RNA ligands to bFGF. 2'-NH₂-modified RNA ligands to bFGF were identified which inhibited the biological activity of bFGF both *in vivo* and *in vitro*. Further included in this invention are single stranded DNA ligands to thrombin and bFGF.

BACKGROUND OF THE INVENTION

Most proteins or small molecules are not known to specifically bind to nucleic acids. The known protein exceptions are those regulatory proteins such as repressors, polymerases, activators and the like which function in a living cell to bring about the transfer of genetic information encoded in the nucleic acids into cellular structures and the replication of the genetic material. Furthermore, small molecules such as GTP bind to some intron RNAs. Living matter has evolved to limit the function of nucleic acids to a largely informational role. The central dogma, as postulated by Crick, both originally and in expanded form, proposes that nucleic acids (either RNA or DNA) can serve as templates for

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the synthesis of other nucleic acids through replicative processes that "read" the information in a template nucleic acid and thus yield complementary nucleic acids. All of the experimental paradigms for genetics and gene expression depend on these properties of nucleic acids: in essence, double-stranded nucleic acids are informationally redundant because of the chemical concept of base pairs and because replicative processes are able to use that base pairing in a relatively error-free manner.

The individual components of proteins, the twenty natural amino acids, possess sufficient chemical differences and activities to provide an enormous breadth of activities for both binding and catalysis. Nucleic acids, however, have been thought to have narrower chemical possibilities than proteins, but to have an informational role that allows genetic information to be passed from virus to virus, cell to cell, and organism to organism. In this context nucleic acid components, the nucleotides, possess only pairs of surfaces that allow informational redundancy within a Watson-Crick base pair. Nucleic acid components need not possess chemical differences and activities sufficient for either a wide range of binding or catalysis.

However, some nucleic acids found in nature do participate in binding to certain target molecules and even a few instances of catalysis have been reported. The range of activities of this kind is narrow compared to proteins and more specifically antibodies. For example, where nucleic acids are known to bind to some protein targets with high affinity and specificity, the binding depends on the exact sequences of nucleotides that comprise the DNA or RNA ligand. Thus, short double-stranded DNA sequences are known to bind to target proteins that repress or activate transcription in both prokaryotes and eukaryotes.

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Other short double-stranded DNA sequences are known to bind to restriction endonucleases, protein targets that can be selected with high affinity and specificity. Other short DNA sequences serve as centromeres and telomeres on chromosomes, presumably by creating ligands for the binding of specific proteins that participate in chromosome mechanics. Thus, double-stranded DNA has a well-known capacity to bind within the nooks and crannies of target proteins whose functions are directed to DNA binding. Single-stranded DNA can also bind to some proteins with high affinity and specificity, although the number of examples is smaller. From the known examples of double-stranded DNA binding proteins, it has become possible to describe some of the binding interactions as involving various protein motifs projecting amino acid side chains into the major groove of B form double-stranded DNA, providing the sequence inspection that allows specificity.

Double-stranded RNA occasionally serves as a ligand for certain proteins, for example, the endonuclease RNase III from *E. coli*. There are more known instances of target proteins that bind to single-stranded RNA ligands, although in these cases the single-stranded RNA often forms a complex three-dimensional shape that includes local regions of intramolecular double-strandedness. The amino-acyl tRNA synthetases bind tightly to tRNA molecules with high specificity. A short region within the genomes of RNA viruses binds tightly and with high specificity to the viral coat proteins. A short sequence of RNA binds to the bacteriophage T4-encoded DNA polymerase, again with high affinity and specificity. Thus, it is possible to find RNA and DNA ligands, either double- or single-stranded, serving as binding partners for specific protein targets. Most known DNA binding proteins bind specifically to double-stranded DNA.

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While most RNA binding proteins recognize single-stranded RNA. This statistical bias in the literature no doubt reflects the present biosphere's statistical predisposition to use DNA as a double-stranded genome and RNA as a single-stranded entity in the roles RNA plays beyond serving as a genome. Chemically there is no strong reason to dismiss single-stranded DNA as a fully able partner for specific protein interactions.

RNA and DNA have also been found to bind to smaller target molecules. Double-stranded DNA binds to various antibiotics, such as actinomycin D. A specific single-stranded RNA binds to the antibiotic thiostreptone; specific RNA sequences and structures probably bind to certain other antibiotics, especially those whose function is to inactivate ribosomes in a target organism. A family of evolutionary related RNAs binds with specificity and decent affinity to nucleotides and nucleosides (Bass, B. and Cech, T. (1984) *Nature* 308:820-826), as well as, to one of the twenty amino acids (Yarus, M. (1986) *Science* 240:1751-1756). Catalytic RNAs are now known as well, although these molecules perform over a narrow range of chemical possibilities, which are thus far related largely to phosphodiester transfer reactions and hydrolysis of nucleic acids.

Despite these known instances, the great majority of proteins and other cellular components are thought not to bind to nucleic acids under physiological conditions and such binding as may be observed is non-specific. Either the capacity of nucleic acids to bind other compounds is limited to the relatively few instances enumerated supra, or the chemical repertoire of the nucleic acids for specific binding is avoided (selected against) in the structures that occur naturally. The present invention is premised on the inventors' fundamental insight that nucleic acids as chemical compounds can form a

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virtually limitless array of shapes, sizes and configurations, and are capable of a far broader repertoire of binding and catalytic functions than those displayed in biological systems.

The chemical interactions have been explored in cases of certain known instances of protein-nucleic acid binding. For example, the size and sequence of the RNA site of bacteriophage R17 coat protein binding has been identified by Uhlenbeck. (Uhlenbeck et al. (1983) *J. Biomol. Structure Dynamics* 1:533 and Romanuk et al. (1987) *Biochemistry* 26:1563) and coworkers. The minimal natural RNA binding site (21 bases long) for the R17 coat protein was determined by subjecting variable-sized labeled fragments of the mRNA to nitrocellulose filter binding assays in which protein-RNA fragment complexes remain bound to the filter (Carey et al. (1983) *Biochemistry* 22:2601). A number of sequence variants of the minimal R17 coat protein binding site were created *in vitro* in order to determine the contributions of individual nucleic acids to protein binding. It was found that the maintenance of the hairpin loop structure of the binding site was essential for protein binding but, in addition, that nucleotide substitutions at most of the single-stranded residues in the binding site, including a bulged nucleotide in the hairpin stem, significantly affected binding. In similar studies, the binding of bacteriophage Q ϕ coat protein to its translational operator was examined (Witcherell and Uhlenbeck (1989) *Biochemistry* 28:71). The Q ϕ coat protein RNA binding site was found to be similar to that of R17 in size, and in predicted secondary structure, in that it comprised about 20 bases with an 8 base pair hairpin structure which included a bulged nucleotide and a 3 base loop. In contrast to the R17 coat protein binding site, only one of the single-stranded residues of the loop is essential for binding and the presence of the

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bulged nucleotide is not required. The protein-RNA binding interactions involved in translational regulation display significant specificity.

Nucleic acids are known to form secondary and tertiary structures in solution. The double-stranded forms of DNA include the so-called B double-helical form, Z-DNA and superhelical twists (Rich, A. et al. (1984) *Ann. Rev. Biochem.* 53:791-846). Single-stranded RNA forms localized regions of secondary structure such as hairpin loops and pseudoknot structures (Schimmel, P. (1989) *Cell* 58:9-12). However, little is known concerning the effects of unpaired loop nucleotides on stability of loop structure, kinetics of formation and denaturation, thermodynamics, and almost nothing is known of tertiary structures and three dimensional shape, nor of the kinetics and thermodynamics of tertiary folding in nucleic acids (Turner, C. et al. (1988) *Proc. Natl. Acad. Sci. USA* 85:1364-1368).

A type of *in vitro* evolution was reported in replication of the RNA bacteriophage Q ϕ . (Mills, D.R. et al. (1967) *Proc. Natl. Acad. Sci. USA* 58:217-224; Levisohn, R. and Spiegelman, S. (1968) *Proc. Natl. Acad. Sci. USA* 60:866-872; Levisohn, R. and Spiegelman, S. (1969) *Proc. Natl. Acad. Sci. USA* 63:805-811; Safhill, R. et al. (1970) *J. Mol. Biol.* 51:531-539; Kacian, D.L. et al. (1972) *Proc. Natl. Acad. Sci. USA* 69:3038-3042; Mills, D.R. et al. (1973) *Science* 180:916-927). The phage RNA serves as a poly-cistronic messenger RNA directing translation of phage-specific proteins and also as a template for its own replication catalyzed by Q ϕ RNA replicase. This RNA replicase was shown to be highly specific for its own RNA templates. During the course of cycles of replication *in vitro* small variant RNAs were isolated which were also replicated by Q ϕ replicase. Minor alterations in the conditions under which cycles of replication were performed were found to result in the accumulation of

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different RNAs, presumably because their replication was favored under the altered conditions. In these experiments, the selected RNA had to be bound efficiently by the replicase to initiate replication and had to serve as a kinetically favored template during elongation of RNA. Kramer et al. (1974) J. Mol. Biol. 82:719 reported the isolation of a mutant RNA template of Q β replicase, the replication of which was more resistant to inhibition by ethidium bromide than the natural template. It was suggested that this mutant was not present in the initial RNA population, but was generated by sequential mutation during cycles of *in vitro* replication with Q β replicase. The only source of variation during selection was the intrinsic error rate during elongation by Q β replicase. In these studies what was termed "selection" occurred by preferential amplification of one or more of a limited number of spontaneous variants of an initially homogeneous RNA sequence. There was no selection of a desired result, only that which was intrinsic to the mode of action of Q β replicase.

Joyce and Robertson (Joyce (1989) in RNA, Catalysis, Splicing, Evolution, Belfort and Shub (eds.), Elsevier, Amsterdam pp. 83-87; and Robertson and Joyce (1990) Nature 344:467-468) reported a method for identifying RNAs which specifically cleave single-stranded DNA. The selection for catalytic activity was based on the ability of the ribozyme to catalyze the cleavage of a substrate ssRNA or DNA at a specific position and transfer the 3'-end of the substrate to the 3'-end of the ribozyme. The product of the desired reaction was selected by using a deoxyoligonucleotide primer which could bind only to the completed product across the junction formed by the catalytic reaction and allowed selective reverse transcription of the ribozyme sequence. The selected catalytic sequences were amplified by attachment of the promoter of T7 RNA

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polymerase to the 3'-end of the cDNA, followed by transcription to RNA. The method was employed to identify from a small number of ribozyme variants the variant that was most reactive for cleavage of a selected substrate.

The prior art has taught or suggested only a limited range of chemical functions for nucleic acids in their interactions with other substances, namely, as targets for proteins that have evolved to bind certain specific oligonucleotide sequences; and more recently, as catalysts with a limited range of activities. Prior "selection" experiments have been limited to a narrow range of variants of a previously described function.

U.S. Patent Application Serial No.

07/536,428, filed June 11, 1990, entitled Systematic Evolution of Ligands by Exponential Enrichment, now abandoned, U.S. Patent No. 5,270,163, issued December 14, 1993, and U.S. Patent Application Serial Number 07/724,131, filed June 10, 1991, both entitled Nucleic Acid Ligands (See also PCT/US91/04078) describe a fundamentally novel method for identifying a nucleic acid ligand for any desired target. Each of these applications, collectively referred to herein as the SHELX Patent Applications, is specifically incorporated herein by reference.

The method of the SHELX Patent Applications is based on the unique insight that nucleic acids have sufficient capacity for forming a variety of two- and three-dimensional structures and sufficient chemical versatility available within their monomers to act as ligands (form specific binding pairs) with virtually any chemical compound, whether large or small in size.

The method involves selection from a mixture of candidates and step-wise iterations of structural improvement, using the same general selection theme, to achieve virtually any desired criterion of binding affinity and selectivity. Starting from a mixture of

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nucleic acids, preferably comprising a segment of randomized sequence, the method, termed SELEX herein, includes steps of contacting the mixture with the target under conditions favorable for binding, partitioning unbound nucleic acids from those nucleic acids which have bound to target molecules, dissociating the nucleic acid-target pairs, amplifying the nucleic acids dissociated from the nucleic acid-target pairs to yield a ligand-enriched mixture of nucleic acids, then reiterating the steps of binding, partitioning, dissociating and amplifying through as many cycles as desired.

While not bound by theory, SELEX is based on the inventors' insight that within a nucleic acid mixture containing a large number of possible sequences and structures there is a wide range of binding affinities for a given target. A nucleic acid mixture comprising, for example, a 20 nucleotide randomized segment can have 4²⁰ candidate possibilities. Those which have the higher affinity constants for the target are most likely to bind to the target. After partitioning, dissociation and amplification, a second nucleic acid mixture is generated, enriched for the higher binding affinity candidates. Additional rounds of selection progressively favor the best ligands until the resulting nucleic acid mixture is predominantly composed of only one or a few sequences. These can then be cloned, sequenced and individually tested for binding affinity as pure ligands.

Cycles of selection and amplification are repeated until a desired goal is achieved. In the most general case, selection/amplification is continued until no significant improvement in binding strength is achieved on repetition of the cycle. The method may be used to sample as many as about 10¹⁴ different nucleic acid species. The nucleic acids of the test mixture preferably include a randomized sequence portion as

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well as conserved sequences necessary for efficient amplification. Nucleic acid sequence variants can be produced in a number of ways including synthesis of randomized nucleic acid sequences and size selection from randomly cleaved cellular nucleic acids. The variable sequence portion may contain fully or partially random sequence; it may also contain subportions of conserved sequence incorporated with randomized sequence. Sequence variation in test nucleic acids can be introduced or increased by mutagenesis before or during the selection/amplification iterations.

In one embodiment of the method of the SELEX Patent Applications, the selection process is so efficient at isolating those nucleic acid ligands that bind most strongly to the selected target, that only one cycle of selection and amplification is required. Such an efficient selection may occur, for example, in a chromatographic-type process wherein the ability of nucleic acids to associate with targets bound on a column operates in such a manner that the column is sufficiently able to allow separation and isolation of the highest affinity nucleic acid ligands.

In many cases, it is not necessarily desirable to perform the iterative steps of SELEX until a single nucleic acid ligand is identified. The target-specific nucleic acid ligand solution may include a family of nucleic acid structures or motifs that have a number of conserved sequences and a number of sequences which can be substituted or added without significantly affecting the affinity of the nucleic acid ligands to the target. By terminating the SELEX process prior to completion, it is possible to determine the sequence of a number of members of the nucleic acid ligand solution family.

A variety of nucleic acid primary, secondary and tertiary structures are known to exist. The

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structures or motifs that have been shown most commonly to be involved in non-Watson-Crick type interactions are referred to as hairpin loops, symmetric and asymmetric bulges, pseudoknots and myriad combinations of the same. Almost all known cases of such motifs suggest that they can be formed in a nucleic acid sequence of no more than 30 nucleotides. For this reason, it is often preferred that SELEX procedures with contiguous randomized segments be initiated with nucleic acid sequences containing a randomized segment of between about 20-50 nucleotides.

The SELEX Patent Applications also describe methods for obtaining nucleic acid ligands that bind to more than one site on the target molecule, and to nucleic acid ligands that include non-nucleic acid species that bind to specific sites on the target. The SELEX method provides means for isolating and identifying nucleic acid ligands which bind to any environment target. However, in preferred embodiments the SELEX method is applied to situations where the target is a protein, including both nucleic acid-binding proteins and proteins not known to bind nucleic acids as part of their biological function.

Basic fibroblast growth factor (bFGF) is a multifunctional effector for many cells of mesenchymal and neuroectodermal origin (Ritkin & Moscatelli (1989) *J. Cell Biol.* 102:1; Baird & Bohlen (1991) in *Peptide Growth Factors and Their Receptors* (Sporn, M. B. & Roberts, A. B., eds.), pp. 369-418, Springer, N.Y.; Basilico & Moscatelli (1992) *Adv. Cancer Res.* 52:115). It is one of the most studied and best characterized members of a family of related proteins that also includes acidic FGF (Uyve et al. (1986) *Science* 233:541; Abraham et al. (1986) *Science* 233:545), int-2 (Moore et al. (1986) *EMBO J.* 5:919), KFGF/hsc/KS3 (Delli Bovi et al. (1987) *Cell* 50:729; Taira et al. (1987) *Proc. Natl. Acad. Sci. USA* 84:2980), FGF-5 (Zhan

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et al. (1988) *Mol. Cell. Biol.* 8:3487), FGF-6 (Marics et al. (1988) *Oncogene* 4:335) and keratinocyte growth factor/FGF-7 (Finch et al. (1989) *Science* 245:752).

In vitro, bFGF stimulates cell proliferation, migration and induction of plasminogen activator and collagenase activities (Presta et al. (1986) *Mol. Cell. Biol.* 6:4060; Moscatelli et al. (1986) *Proc. Natl. Acad. Sci. USA* 83:2091; Mignatti et al. (1989) *J. Cell Biol.* 108:671). *In vivo*, it is one of the most potent inducers of neovascularization. Its angiogenic activity *in vivo* suggests a role in tissue remodeling and wound healing, but also, in some disease states that are characterized by pathological neovascularization such as tumor proliferation, tumor metastasis, diabetic retinopathy and rheumatoid arthritis (Polman & Klagsbrun (1987) *Science* 235:442; Gospodarowicz (1991) *Cell Biology Reviews* 25:307).

Although bFGF does not have a signal sequence for secretion, it is found on both sides of the plasma membrane, presumably being exported via exocytosis (Vlodavsky et al. (1991) *Trends Biol. Sci.* 16:268; Mignatti & Ritkin (1991) *J. Cell. Biochem.* 47:201). In the extracellular matrix, it is typically associated with a fraction that contains heparan sulfate proteoglycans. Indeed, heparin affinity chromatography has been a useful method for purification of this and other heparin-binding growth factors. Heparin is a glycosaminoglycan composed of chains of alternating residues of D-glucosamine and uronic acid. In cell culture, bFGF binds to low- and high-affinity sites.

The low-affinity sites are composed of cell-associated heparan sulfate proteoglycans to which bFGF binds with approximately nanomolar affinity (Moscatelli (1987) *J. Cell. Physiol.* 131:123). All biological effects of bFGF are mediated through interaction with the high-affinity binding sites (10-100 pM) that represent the dimeric tyrosine kinase FGF receptor (Ueno et al.

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(1992) J. Biol. Chem. 267:1470).

Five FGF receptor genes have been identified to date, each of which can produce several structural variants as a result of alternative mRNA splicing (Armstrong et al. (1992) Cancer Res. 52:2004; Ueno et al. (1992) J. Biol. Chem. 267:1470). There is substantial evidence that the low- and the high-affinity binding sites act cooperatively in determining the overall affinity of bFGF. Experiments with mutant cell lines that are deficient in glycosaminoglycan synthesis (Yayon et al. (1991) Cell 64:841) or heparitinase treated cells (Rapraeger et al. (1991) Science 252:1705) have shown that binding of either cell-associated heparan sulfate or, in its absence, exogenously added heparin to bFGF is required for signaling via the tyrosine kinase receptor. Recent resolution of observed K_d into its kinetic components demonstrates that while the association rates of bFGF to the low- and the high-affinity sites are comparable, the dissociation rate of bFGF from the cell surface receptor is 23-fold slower than that for the cell-associated heparan sulfate (Nugent & Edelman (1992) Biochemistry 31:8876). The slower off-rate, however, is only observed when the receptor is bound to the cell surface suggesting that simultaneous binding to both sites contributes to the overall high-affinity binding. This is plausible in light of the observation that the heparin-binding and the receptor-binding sites are located on adjacent, but separate regions of the molecule, as determined from the recently solved X-ray crystal structure of bFGF (Zhang et al. (1991) Proc. Natl. Acad. Sci. USA 88:3446; Eriksson et al. (1991) Proc. Natl. Acad. Sci. USA 88:3441; Ago et al. (1991) J. Biochem. 110:350; Zhu et al. (1991) Science 251:90).

The idea that bFGF antagonists may have useful medicinal applications is not new (reviewed in Gospodarowicz (1991) Cell Biology Reviews 25:307).

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bFGF is now known to play a key role in the development of smooth-muscle cell lesions following vascular injury (Reidy et al. (1992) Circulation, Suppl. III 86:III-43). Overexpression of bFGF (and other members of the FGF family) is correlated with many malignant disorders (Hatahan et al. (1991) Ann. N. Y. Acad. Sci. 618:232; Takahashi et al. (1990) Proc. Natl. Acad. Sci. USA 87:5710; Fujimoto et al. (1991) Biochem. Biophys. Res. Commun. 180:386) and recently, neutralizing anti-bFGF antibodies have been found to suppress solid tumor growth in vivo by inhibiting tumor-linked angiogenesis (Hori et al. (1991) Cancer Res. 51:6180). Notable in this regard is the recent therapeutic examination of suramin, a polysulfated naphthalene derivative with known antiparasitic activity, as an anti-tumor agent. Suramin is believed to inhibit the activity of bFGF through binding in the polyanion binding site and disrupting interaction of the growth factor with its receptor (Maddaugh et al. (1992) Biochemistry 31:9016; Eriksson et al. (1991) Proc. Natl. Acad. Sci. USA 88:3441). In addition to having a number of undesirable side effects and substantial toxicity, suramin is known to interact with several other heparin-binding growth factors which makes linking of its beneficial therapeutic effects to specific drug-protein interactions difficult (La Rocca et al. (1990) Cancer Cells 2:106). Anti-angiogenic properties of certain heparin preparations have also been observed (Folkman et al. (1983) Science 221:719; Crum et al. (1985) Science 230:1375) and these effects are probably based at least in part on their ability to interfere with bFGF signaling. While the specific heparin fraction that contributes to bFGF binding is now partially elucidated (Ishai-Michaeli et al. (1992) Biochemistry 31:2080; Turnbull et al. (1992) J. Biol. Chem. 267:10337), a typical heparin preparation is heterogeneous with respect to size, degree of sulfation

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and iduronic acid content. Additionally, heparin also affects many enzymes and growth factors. Excluding monoclonal antibodies, therefore, specific antagonists of bFGF are not known.

Thrombin is a multifunctional serine protease that has important procoagulant and anticoagulant activities. As a procoagulant enzyme thrombin cleaves fibrinogen, activates clotting factors V, VIII, and XIII, and activates platelets. The specific cleavage of fibrinogen by thrombin initiates the polymerization of fibrin monomers, a primary event in blood clot formation. The central event in the formation of platelet thrombi is the activation of platelets from the "nonbinding" to the "binding" mode and thrombin is the most potent physiologic activator of platelet aggregation (Bernat and Phillips (1991) in Platelets in Biology and Pathology, J.L. Gordon, ed. (Amsterdam:Elsevier/North Holland Biomedical Press), pp. 43-74; Hansen and Harker (1988) *Proc. Natl. Acad. Sci. USA* 85:3184-3188; Bidt et al. (1989) *J. Clin. Invest.* 84:18-27). Thus, as a procoagulant, thrombin plays a key role in the arrest of bleeding (physiologic hemostasis) and formation of vasocclusive thrombi (pathologic thrombosis).

As an anticoagulant thrombin binds to thrombomodulin (TM), a glycoprotein expressed on the surface of vascular endothelial cells. TM alters substrate specificity from fibrinogen and platelets to protein C through a combination of an allosteric change in the active site conformation and an overlap of the TM and fibrinogen binding sites on thrombin. Activated protein C, in the presence of a phospholipid surface, Ca^{2+} , and a second vitamin K-dependent protein cofactor, protein S, inhibits coagulation by proteolytically degrading factors Va and VIIIa. Thus, the formation of the thrombin-TM complex converts thrombin from a procoagulant to an anticoagulant

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enzyme, and the normal balance between these opposing activities is critical to the regulation of hemostasis.

Thrombin is also involved in biological responses that are far removed from the clotting system (reviewed in Zimmerman et al. (1986) *Ann. N. Y. Acad. Sci.* 485:349-368; Marx (1992) *Science* 256:1278-1280). Thrombin is chemotactic for monocytes (Bar-Shavit et al. (1983) *Science* 220:728-730), mitogenic for lymphocytes (Chen et al. (1976) *Exp. Cell Res.* 101:41-46), mesenchymal cells (Chen and Buchanan (1975) *Proc. Natl. Acad. Sci. USA* 72:131-138), and fibroblasts (Marx (1992) *Science* 256:1278-1280). Thrombin activates endothelial cells to express the neutrophil adhesive protein GMP-140 (PADGEM) (Hactori et al. (1989) *J. Biol. Chem.* 264:7768-7771) and produce platelet-derived growth factor (Daniel et al. (1986) *J. Biol. Chem.* 261:9579-9582). Recently it has been shown that thrombin causes cultured nerve cells to retract their neurites (reviewed in Marx (1992) *Science* 256:1278-1280).

The mechanism by which thrombin activates platelets and endothelial cells is through a functional thrombin receptor found on these cells. A putative thrombin cleavage site (LDR/S) in the receptor suggests that the thrombin receptor is activated by proteolytic cleavage of the receptor. This cleavage event "unmasks" an N-terminal domain which then acts as the ligand, activating the receptor (Vu et al. (1991) *Cell* 64:1057-1068).

Vascular injury and thrombus formation represent the key events in the pathogenesis of various vascular diseases, including atherosclerosis. The pathogenic processes of the activation of platelets and/or the clotting system leading to thrombosis in various disease states and in various sites, such as the coronary arteries, cardiac chambers, and prosthetic heart valves, appear to be different. Therefore, the

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use of a platelet inhibitor, an anticoagulant, or a combination of both may be required in conjunction with thrombolytics to open closed vessels and prevent reocclusion.

5 Controlled proteolysis by compounds of the coagulation cascade is critical for hemostasis. As a result, a variety of complex regulatory systems exist that are based, in part, on a series of highly specific protease inhibitors. In a pathological situation functional inhibitory activity can be interrupted by excessive production of active protease or inactivation of inhibitory activity. Perpetuation of inflammation in response to multiple trauma (tissue damage) or infection (sepsis) depends on proteolytic enzymes, both of plasma cascade systems, including thrombin, and lysosomal origin. Multiple organ failure (MOF) in these cases is enhanced by the concurrently arising imbalance between proteases and their inhibitory regulators. An imbalance of thrombin activity in the brain may lead to neurodegenerative diseases.

20 Thrombin is naturally inhibited in hemostasis by binding to antithrombin III (ATIII), in a heparin-dependent reaction. Heparin exerts its effect through its ability to accelerate the action of ATIII. In the brain, protease nexin (PN-1) may be the natural inhibitor of thrombin to regulate neurite outgrowth.

25 As stated above, heparin is a glycosaminoglycan composed of chains of alternating residues of D-glucosamine and uronic acid. Its anticoagulant effect is mediated through its interaction with ATIII. When heparin binds ATIII, the conformation of ATIII is altered, and it becomes a significantly enhanced inhibitor of thrombin. Although heparin is generally considered to be effective for certain indications, it is believed that the physical size of the ATIII-heparin complex prevents access to much of the biologically active thrombin in the body,

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thus diminishing its ability to inhibit clot formation. Side effects of heparin include bleeding, thrombocytopenia, osteoporosis, skin necrosis, alpe, hypersensitivity and hypoadosteronism.

5 Hirudin is a potent peptide inhibitor of thrombin derived from the European medicinal leech *Hirudo medicinalis*. Hirudin inhibits all known functions of α -thrombin, and has been shown to bind thrombin at two separate sites kinetically; a high affinity site at or near the catalytic site for serine protease activity and a second anionic exosite. The anionic exosite also binds fibrinogen, heparin, TM and probably the receptor involved in mediating the activation of platelets and endothelial cells. A C-terminal hirudin peptide -- which has been shown by co-crystallization with thrombin to bind in the anionic exosite -- has inhibitory effects on fibrin formation, platelet and endothelial cell activation, and Protein C activation via TM binding, presumably by competing for binding at this site. This peptide does not inhibit proteolytic activity towards tripeptide chromogenic substrates, Factor V or X.

20 The structure of thrombin makes it a particularly desirable target for nucleic acid binding, due to the anionic exosite. Site-directed mutagenesis within this site has shown that fibrinogen-clotting and TM binding activities are separable. Conceivably, an RNA ligand could be selected that has procoagulatory and/or anticoagulatory effects depending on how it interacts with thrombin, i.e., which substrate it mimics.

30 A single stranded DNA ligand to thrombin has been prepared according to a procedure identical to SELEX. See, Bock et al. (1993) Nature 355:564-565. A consensus ligand was identified after relatively few rounds of SELEX were performed, that was shown to have some ability to prevent clot formation in vitro. The

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ligand is the 15mer DNA 5'-GGTGGTGTGTGG-3', referred to herein as G15D (SEQ ID NO:189). The symmetrical nature of the primary sequence suggests that G15D has a regular fixed tertiary structure. The K_d of G15D to thrombin is about 2×10^{-7} . For effective thrombin inhibition as an anticoagulant, the stronger the affinity of the ligand to thrombin the better.

SUMMARY OF THE INVENTION

The present invention includes methods for identifying and producing nucleic acid ligands and the nucleic acid ligands so identified and produced. Nucleic acid sequences are provided that are ligands of bFGF and thrombin. Specifically, RNA and DNA sequences are provided that are capable of binding specifically to bFGF and to thrombin. Included within the invention are the nucleic acid ligand sequences shown in Tables II-IV (SEQ ID NOS:6-69), Table VIII (SEQ ID NOS:101-185), Tables XII-XIII (SEQ ID NOS:192-214), Table XV-XVII (SEQ ID NOS:216-319) and XXI-XXII (SEQ ID NOS:330-445).

Also included in this invention are nucleic acid ligands of bFGF that are inhibitors of bFGF. Specifically, RNA ligands are identified and described which inhibit the binding of bFGF to its receptors.

Further included in this invention is a method of identifying nucleic acid ligands and ligand sequences to bFGF and thrombin comprising the steps of a) preparing a candidate mixture of nucleic acids; b) partitioning between members of said candidate mixture on the basis of affinity to bFGF or thrombin; and c) amplifying the selected molecules to yield a mixture of nucleic acids enriched for nucleic acid sequences with a relatively higher affinity for binding to bFGF or thrombin.

More specifically, the present invention includes the RNA ligands to bFGF and to thrombin

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identified according to the above-described method, including those ligands listed in Tables II-IV and Tables XII and XIII. Also included are RNA ligands to bFGF and thrombin that are substantially homologous to any of the given ligands and that have substantially the same ability to bind and inhibit bFGF and thrombin. Further included in this invention are RNA ligands to bFGF and thrombin that have substantially the same structural form as the ligands presented herein and that have substantially the same ability to bind and inhibit bFGF and thrombin.

The present invention also includes modified nucleotide sequences based on the nucleic acid ligand sequences identified herein and mixtures of the same. Specifically included in this invention are RNA ligands, that have been modified at the ribose and/or phosphate and/or base positions to increase the *in vivo* stability of the RNA ligand. Other modification to RNA ligands are encompassed by this invention, including specific alterations in base sequence, and additions of nucleic acids or non-nucleic acid moieties to the original compound. More specifically, included in this invention are the RNA ligands to bFGF, comprising nucleotides modified at the 2'-amino (2'-NH₂) position shown in Table VIII. The 2'-NH₂-modified RNA ligands possess improved *in vivo* stability.

The SELAX method utilizing a single-stranded DNA library of nucleic acids was also performed using bFGF and thrombin as the target. Included within the invention, therefore, are the single-stranded DNA ligands to bFGF shown in Tables XXI and XXII and to thrombin shown in Tables XV and XVI. Also included in the invention are DNA ligands to thrombin that are substantially homologous to the DNA ligands identified herein and that have substantially the same ability to bind thrombin. Further included in this invention are DNA ligands to thrombin that have substantially the

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same structural form as the DNA ligands presented herein and that have substantially the same ability to bind thrombin.

5 BRIEF DESCRIPTION OF THE FIGURES

Figure 1 shows binding curves for bPGF Family 1 ligand 7A (SEQ ID NO:10) (Δ), Family 2 ligand 12A (SEQ ID NO:25) (\square), random RNA, SELEX experiment A (+) and random RNA, SELEX experiment B (x). The fraction of RNA bound to nitrocellulose filters is plotted as a function of free protein concentration and data points were fitted to equation 2 as defined in Example 3 below. The following concentrations of RNA were used: < 100 pM for 7A and 12A, and 10 nM for random RNAs. Binding reactions were done at 37 °C in phosphate buffered saline containing 0.01% human serum albumin.

Figure 2 shows the effect of bPGF RNA ligands 5A (SEQ ID NO:9) (\circ), 7A (SEQ ID NO:10) (Δ), 12A (SEQ ID NO:25) (\square), 26A (SEQ ID NO:26) (\diamond), random RNA, SELEX experiment A (+) and random RNA, SELEX experiment B (x) on binding of 32 P-bPGF to the low-affinity (Figure 2A) and the high-affinity (Figure 2B) cell-surface receptors. Experiments were done essentially as described in Roghani & Moscatelli (1992) J. Biol. Chem. 267:22156.

Figure 3 shows the competitive displacement of 32 P-labeled bPGF RNA ligands 5A (SEQ ID NO:9) (\circ), 7A (SEQ ID NO:10) (Δ), 12A (SEQ ID NO:25) (\square), and 26A (SEQ ID NO:26) (\diamond) by heparin (average molecular weight 5,000 Da). Percent of total input RNA bound to nitrocellulose filters is plotted as a function of heparin concentration. Experiments were done at 37 °C in phosphate buffered saline containing 0.01% human serum albumin, 0.3 μ M RNA, and 30 nM bPGF.

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Figure 4 shows the consensus structures for bPGF Family 1 and Family 2 ligands. Y = C or U; R = A or G; W = A or U; H = A, U, or C; D = A, G, or U; N = any base. Complementary bases are primed. Symbols in parentheses indicate a variable number of bases or base pairs at that position ranging within limits given in the subscript.

Figure 5 shows the binding curves for 2'-NH₂ modified bPGF RNA ligands 21A (SEQ ID NO:104) (\circ) (SELEX experiment A), 38B (SEQ ID NO:114) (Δ) (SELEX experiment B) and the initial (random) RNAs (A and B) from which these ligands were selected (\square , \diamond).

Figure 6 shows 2'-NH₂-modified bPGF RNA ligand inhibition of 32 P-bPGF binding to the low-affinity (Figure 6A) and the high-affinity (Figure 6B) cell surface receptors. The ligands tested were 21A (SEQ ID NO:104) (Δ), 21A-t (SEQ ID NO:186) (\circ), and random RNA A (\diamond).

Figure 7 shows the possible secondary structures of the 76 nucleotide Class I thrombin RNA clones 6 (SEQ ID NO:211), 16 (SEQ ID NO:212), and 18 (SEQ ID NO:213), and the Class II 72 nucleotide clone 27 (SEQ ID NO:214) as determined from boundary experiments. Boundaries are underlined. The 5' and 3' fixed regions are depicted by small case lettering, the 30N random region by caps and the conserved region by bold caps. The hairpin structures that were synthesized are boxed with the total number of nucleotides indicated.

Figure 8 depicts binding curves for various thrombin ligands. In Figure 8A RNAs with unique 30N sequence motifs (see Table XII) were chosen for binding analysis with human thrombin (Sigma), including the

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three from Class I: RNA 6 (SEQ ID NO:192), RNA 16 (SEQ ID NO:198), and RNA 18 (SEQ ID NO:199), and one from Class II: RNA 27 (SEQ ID NO:209). Binding of bulk RNA sequences of the 30N3 candidate mixture is also shown. In Figure 8B, binding of class I RNA clones 6, 16, 18 and Class II RNA clone 27 is shown, but with human thrombin from Enzyme Research Laboratories. In Figure 8C, binding of the 15mer ssDNA 5'-GGTGGTGTGGTGG-3' (G15D) (SEQ ID NO:189), the Class I clone 16 hairpin structures (24R, 39D) (SEQ ID NO:212) and the Class II clone 27 hairpin structure (33R) (SEQ ID NO:214) (see Figure 7 and Table XIII) are shown under identical conditions as in Figure 8B. In the case of the RNA hairpin structures, R denotes RNA synthesis and D denotes transcription from a DNA template.

Figure 9 depicts a binding comparison of thrombin RNA ligands between unmodified RNA and RNA with pyrimidines modified to contain the 2'-NH₂ ribose nucleotide. Figure 9A depicts the binding comparison of bulk RNA 30N candidate mixture and 2'-NH₂ modified 30N candidate mixture. Figure 9B depicts the binding comparison of Class I RNA 16 (SEQ ID NO:198) and 2'-NH₂ modified RNA 16, and Figure 11C depicts the binding comparison of Class II RNA 27 (SEQ ID NO:209) and 2'-NH₂ modified RNA 27 are shown.

Figure 10 depicts the competition experiments between the 15mer ssDNA G15D (SEQ ID NO:189) and the thrombin RNA hairpin ligands of this invention for binding to human thrombin. In Figure 10A the concentration of the tracer G15D is equal to the concentration of protein at 1 μ M. The competitors for binding include G15D itself, the 24 and 39 nucleotide RNA hairpin structures from Class I RNA 16 (SEQ ID NO:212), and the 33 nucleotide RNA hairpin structure from Class II RNA 27 (SEQ ID NO:214) (see Figure 7).

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Binding is expressed as the relative fraction G15D bound, which is the ratio of G15D binding with competitor to G15D binding without competitor. In Figure 10B 33 nucleotide hairpin RNA is the tracer and the concentration of the tracer is equal to the concentration of protein at 300 nM. The competitors for binding include the ssDNA G15D and RNA 24.

Figures 11A and 11B show specificity of binding for thrombin ligands. Class I RNA 16 (SEQ ID NO:198), Class II RNA 27 (SEQ ID NO:209), and bulk 30N3 RNA were chosen for binding analysis with human antithrombin III (Sigma) (Figure 11A) and human prothrombin (Sigma) (Figure 11B).

Figure 12 shows the results of nitrocellulose filter binding assays for the 30N and 60N DNA candidate mixtures and the nucleic acid pools, both 30N and 60N, after performing 11 rounds of SELEX to thrombin.

Figure 13 depicts the binding curve for the truncated thrombin DNA ligand referred to as 60-18(38) (SEQ ID NO:278) and the binding curve for the non-truncated form of the same DNA ligand, 60-18 (SEQ ID NO:279).

Figure 14 depicts the results of the thrombin DNA ligand 60-18(38) (SEQ ID NO:278) in the clot inhibition assay.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

This application is an extension and an application of the method for identifying nucleic acid ligands referred to as SELEX. The SELEX method is described in detail in U.S. patent application serial number 07/714,131, filed June 10, 1991, entitled Nucleic Acid Ligands, 07/536,428, filed June 11, 1990,

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entitled Systematic Evolution of Ligands by EXponential
Enrichment, now abandoned, 07/931,473 filed August 17,
1992, now United States Patent No. 5,270,163, entitled
Nucleic Acid Ligands. These applications are
collectively referred to herein as the SELEX
Applications. The full text of these applications,
including but not limited to, all definitions and
descriptions of the SELEX process, are specifically
incorporated herein by reference.

10 In its most basic form, the SELEX process may
be defined by the following series of steps:

15 1) A candidate mixture of nucleic acids of
differing sequence is prepared. The candidate mixture
generally includes regions of fixed sequences (i.e.,
each of the members of the candidate mixture contains
the same sequences in the same location) and regions of
randomized sequences. The fixed sequence regions are
selected either: a) to assist in the amplification
steps described below; b) to mimic a sequence known to
bind to the target; or c) to enhance the concentration
of a given structural arrangement of the nucleic acids
in the candidate mixture. The randomized sequences can
be totally randomized (i.e., the probability of finding
a base at any position being one in four) or only
partially randomized (i.e., the probability of finding
a base at any location can be selected at any level
between 0 and 100 percent).

20 2) The candidate mixture is contacted with
the selected target under conditions favorable for
binding between the target and members of the candidate
mixture. Under these circumstances, the interaction
between the target and the nucleic acids of the
candidate mixture can be considered as forming nucleic
acid-target pairs between the target and the nucleic
acids having the strongest affinity for the target.
3) The nucleic acids with the highest
affinity for the target are partitioned from those

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nucleic acids with lesser affinity to the target.
Because only an extremely small number of sequences
(and possibly only one molecule of nucleic acid)
corresponding to the highest affinity nucleic acids
exist in the candidate mixture, it is generally
desirable to set the partitioning criteria so that a
significant amount of the nucleic acids in the
candidate mixture (approximately 5-50%) are retained
during partitioning.

10 4) Those nucleic acids selected during
partitioning as having the relatively higher affinity
to the target are then amplified to create a new
candidate mixture that is enriched in nucleic acids
having a relatively higher affinity for the target.

15 5) By repeating the partitioning and
amplifying steps above, the newly formed candidate
mixture contains fewer and fewer unique sequences, and
the average degree of affinity of the nucleic acids to
the target will generally increase. Taken to its
extreme, the SELEX process will yield a candidate
mixture containing one or a small number of unique
nucleic acids representing those nucleic acids from the
original candidate mixture having the highest affinity
to the target molecule.

20 The SELEX Patent Applications describe and
elaborate on this process in great detail. Included
are targets that can be used in the process; methods
for the preparation of the initial candidate mixture;
methods for partitioning nucleic acids within a
candidate mixture; and methods for amplifying
partitioned nucleic acids to generate enriched
candidate mixtures. The SELEX Patent Applications also
describe ligand solutions obtained to a number of
target species, including both protein targets wherein
the protein is and is not a nucleic acid binding
protein.

SELEX provides high affinity ligands of a

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target molecule. This represents a singular achievement that is unprecedented in the field of nucleic acids research. The present invention applies the SILEX procedure to the specific targets, bFGF and thrombin. In the Example section below, the experimental parameters used to isolate and identify the nucleic acid ligand solutions to bFGF and thrombin are described.

In order to produce nucleic acids desirable for use as a pharmaceutical, it is preferred that the nucleic acid ligand 1) binds to the target in a manner capable of achieving the desired effect on the target; 2) be as small as possible to obtain the desired effect; 3) be as stable as possible; and 4) be a specific ligand to the chosen target. In most, if not all situations, it is preferred that the nucleic acid ligand have the highest possible affinity to the target.

In co-pending and commonly assigned U.S. Patent Application Serial No. 07/964,624, filed October 21, 1992, methods are described for obtaining improved nucleic acid ligands after SILEX has been performed. This application, entitled Methods of Producing Nucleic Acid Ligands is specifically incorporated herein by reference. Included in this application are methods relating to assays of ligand effects on target molecules; affinity assays of the ligands; information boundaries determination; quantitative and qualitative assessment of individual nucleotide contributions to affinity via secondary SILEX, nucleotide substitution, and chemical modification experiments; and structural determination. The present invention includes improvements to the nucleic acid ligand solutions derived according to these procedures.

This invention includes the specific nucleic acid ligands shown in Tables II-IV, Table VIII, Tables XII-XIII, Tables XV-XVIII and Tables XXI-XXII. These

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Tables include unmodified RNA ligands to bFGF (Tables II-IV (SEQ ID NOS:8-69)), modified RNA ligands to bFGF (Table VIII (SEQ ID NOS:101-185)), DNA ligands to bFGF (Tables XII-XXII (SEQ ID NOS:330-445)), unmodified RNA ligands to thrombin (Tables XII-XIII (SEQ ID NOS:192-214)) and DNA ligands to thrombin (Tables XV-XVIII (SEQ ID NOS:216-319)) identified by the SILEX method as described herein. The scope of the ligands covered by this invention extends to all ligands to bFGF and thrombin identified according to the SILEX procedure. More specifically, this invention includes nucleic acid sequences that are substantially homologous to and that have substantially the same ability to bind bFGF and thrombin as the specific nucleic acid ligands shown in Tables II-IV, VII, XII-XIII, XV-XVIII and XXI-XXII. By substantially homologous, it is meant, a degree of primary sequence homology in excess of 70%, most preferably in excess of 80%. Substantially the same ability to bind bFGF or thrombin means that the affinity is within two orders of magnitude of the affinity of the ligands described herein. It is well within the skill of those of ordinary skill in the art to determine whether a given sequence -- substantially homologous to those specifically described herein -- has substantially the same ability to bind bFGF or thrombin.

A review of the proposed structural formations shown in Figure 4 for the Family 1 and 2 unmodified ligands to bFGF and Figure 7 for the Class 1 and 2 unmodified ligands to thrombin shows that sequences that have little or no primary sequence homology may still have substantially the same ability to bind bFGF or thrombin, respectively. It can be assumed that the disparate sequences in Figure 4 have similar structures that give rise to the ability to bind to bFGF, and that each of the Family 1 and Family 2 sequence ligands are able to assume structures that

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appear very similar to the binding site of bFGF even though they may not bind the same site. Likewise, it can be assumed that the disparate sequences depicted in Figure 7 have a common structure that gives rise to the ability to bind to thrombin, and that each of the Class 1 and Class 2 sequence ligands are able to assume structures that appear very similar to the binding site of thrombin even though they may not bind the same site. For these reasons, the present invention also includes RNA ligands that have substantially the same structure as the ligands presented herein and that have substantially the same ability to bind bFGF and thrombin as the RNA ligands shown in Tables II and III and Table XII, respectively. "Substantially the same structure" includes all RNA ligands having the common structural elements of the sequences given in Tables II, III and XII.

As stated above, this invention also includes the specific 2'-NH₂-modified nucleic acid ligands to bFGF shown in Table VIII. These ligands were identified by the SELEX method utilizing a candidate mixture of RNAs wherein all pyrimidines were 2'-deoxy-2'-NH₂. All purines utilized in these experiments were unmodified, or 2'-OH. More specifically, this invention includes nucleic acid sequences that are substantially homologous to and that have substantially the same ability to bind bFGF as the specific nucleic acid ligands shown in Table VIII.

This invention also covers the specific DNA nucleic acid ligands to bFGF (Tables XXI and XXII) and thrombin (Tables XV and XVI). Also included are DNA sequences that are substantially homologous to and that have substantially the same ability to bind thrombin and bFGF as the specific sequences given in Tables XV, XVI, XXI and XXII. Also included are DNA ligands that have substantially the same structure as the ligands presented in Tables XV, XVI, XXI and XXII and that have

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substantially the same ability to bind thrombin and bFGF, respectively.

This invention also includes the ligands described above, wherein certain chemical modifications have been made in order to increase the *in vivo* stability of the ligand, enhance or mediate the delivery of the ligand, or reduce the clearance rate from the body. Examples of such modifications include chemical substitutions at the ribose and/or phosphate and/or base positions of a given RNA sequence. See, e.g., Cook et al. PCT Application WO 92/03568; U.S. Patent No. 5,118,672 of Schinazi et al.; Hobbs et al. (1973) Biochem. J. 138; Guethbauer et al. (1977) Nucleic Acids Res. 4:1933; Shibahara et al. (1987) Nucleic Acids Res. 15:4403; Pleken et al. (1991) Science 253:314, each of which is specifically incorporated herein by reference. Such modifications may be made post-SELEX (modification of previously identified unmodified ligands) or by incorporation into the SELEX process as described below.

Two SELEX experiments were conducted to select unmodified RNA ligands to bFGF (Examples 1 and 2). These experiments yielded two sequence families of high-affinity nucleic acid ligands to bFGF Family 1 and Family 2 (Tables II and III), as well as single sequences ("other sequences") (Table IV) and repeat sequences (Table V). A review of the two sequence families (Tables II and III) shows that sequences that have little or no primary sequence homology may still have substantially the same ability to bind bFGF. It appears that the disparate sequences may have a common structure that gives rise to the ability to bind to bFGF, and that each of the sequence Family 1 and 2 ligands are able to assume structures that appear very similar to the binding site of bFGF even though they may not bind the same site. High-affinity nucleic acid ligands selected in the presence of heparin (Experiment

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B) exhibited the consensus sequence of Family 2. These ligands bind a bFGF protein in which a conformation change has been induced by heparin.

The high-affinity nucleic acid ligands to bFGF of the present invention may also have various properties, including the ability to inhibit the biological activity of bFGF. Representative ligands from Family 1 and 2 (Tables II and III) were found to inhibit binding of bFGF to both low-and high-affinity cell-surface receptors (Example 5). These nucleic acid ligands may be useful as specific and potent neutralizers of bFGF activity *in vivo*.

Two SELEX experiments, to select ligands to bFGF, were conducted with RNA candidate mixtures wherein all pyrimidine moieties were 2'-deoxy-2'-NH₂-pyrimidines (Example 4, experiments A and B). These experiments yielded the sequences shown in Table VIII. Sequence families 1A, 1B, 1C, 2 and 3 were identified, as well as, four families containing two sequences each ("two-member families"), single sequences ("other sequences"), and sequences binding nitrocellulose ("nitrocellulose-binding family"). The nitrocellulose-binding ligands have an increased affinity to nitrocellulose as well as an increased affinity to bFGF. The high affinity of identified 2'-NH₂ ligands for bFGF is shown in Table IX and Figure 5. 2'-NH₂-modified RNA ligands able to inhibit the *in vitro* activity of bFGF were identified (Figure 6). These ligands were shown to inhibit the biological activity of bFGF *in vivo* (Example 6).

The effect of the modified 2'-NH₂ RNA ligands on endothelial cell motility was examined in Example 7. Ligand 21A-ts (SEQ ID NO:444), a chemically synthesized analogue of ligand 22A-t (SEQ ID NO:186), was found to inhibit bovine aortic endothelial (BAE) cell migration in a dose dependent manner at concentrations greater than 50 nM. The total amount of motility that could be

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inhibited by 21A-ts at high concentrations was comparable in all experiments to the effect of 100 µg/ml neutralizing bFGF antibody.

Example 8 describes the evolution of high affinity DNA ligands to bFGF using SELEX (see Table XXI). Candidate mixtures with 30 and 40 variable nucleotide regions were employed in three experiments starting with three separate sets of synthetic DNA oligonucleotide templates and primers (see Table XIX). A significant improvement in affinity of DNA ligands to bFGF was observed in each of the three experiments after ten rounds of selection (see Table XX in which the results for Experiment 3 are depicted). Five distinct families were identified based on 40% or better overlap in sequence homology (Table XXI). A number of sequences with no homology to members of the five families were also present and are listed in Table XXI as orphans.

A majority of the ligands isolated from Experiments 1 and 3 were screened for their ability to bind bFGF and high-affinity ligands for bFGF were found in five sequence families (see Example 8 and Table XXI (*)). The K_{ds} of the isolates tested for affinity to bFGF are listed in Table XXII. Removal of nucleotides non-essential for binding was performed on five of the ligands with the highest affinity for bFGF, K_{ds} less than 1 nM (Table XXII, Truncations).

The five truncated molecules were tested for their ability to inhibit binding of bFGF to its low- and high-affinity cell-surface receptors. All five ligands show inhibition in the nanomolar range.

Truncated ligand M225t3 (SEQ ID NO:364) was also tested for its specificity. It was found that the affinity of M225t3 for vascular endothelial growth factor and human chorionic gonadotropin, two heparin-binding proteins, was relatively weak (K_d > 0.2 µM).

To determine whether enhanced circulation

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time could be obtained by conjugating the bFGF ligand to a high molecular weight species, a M25tc3 DNA ligand was synthesized and coupled with an N-hydroxysuccinimide active ester of PEG 3400 [Example 9]. The PEG modified M25tc3 was shown to bind bFGF with a similar affinity as the non-modified ligand.

The nucleic acid ligands and nucleic acid ligand solutions to bFGF described herein are useful as pharmaceuticals, and as part of gene therapy treatments. Example 6 shows the ability of 2'-NH₂-modified RNA ligands to inhibit the *in vivo* biological activity of bFGF. Further, the nucleic acid ligands to bFGF described herein may be used beneficially for diagnostic purposes.

15 The SELEX process for identifying ligands to a target was performed using human thrombin as the target, and a candidate mixture containing 76 nucleotide RNAs with a 30 nucleotide region of unmodified randomized sequences (Example 10).
20 Following twelve rounds of SELEX, a number of the selected ligands were sequenced, to reveal the existence of two groups of sequences that had common elements of primary sequence (Example 11).

25 A dramatic shift in binding of the RNA population was observed after 12 rounds of SELEX, when compared to the bulk 30N RNA. Sequencing of bulk RNA after 12 rounds also showed a non-random sequence profile. The RNA was reverse transcribed, amplified, cloned and the sequences of 28 individual molecules were determined (Table XII). Each sequence is divided
30 into 3 blocks from left to right: 1) the 5' fixed region, 2) the 30N variable region, and 3) the 3' fixed region. Based on primary sequence homology, 22 of the RNAs were grouped as Class I and 6 RNAs were grouped as Class II. Of the 22 sequences in Class I, 16 (8 of which were identical) contained an identical sequence motif GGAUCCAGAG(N)₁₆GUAGGC (SEQ ID NO:190), whereas the

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remaining 6 contained 1 or 2 nucleotide changes in the defined region or some variation in N=2 to N=5. This conserved motif varied in its position within the 30N region. In Class II, 3 of the 6 RNAs were identical and all of them contained the conserved motif GCGGCUUGGCGGCGGCUU (SEQ ID NO:191), beginning at the 3rd nucleotide from the end of the 5' fixed region.

Three sequence variant RNA ligands from Class I (6 (SEQ ID NO:192), 16 (SEQ ID NO:198), and 18 (SEQ ID NO:199)) and one (27 (SEQ ID NO:209)) from Class II, identified by the order they were sequenced, were used for individual binding analysis. Class I RNAs were exemplified by clone 16 with a K_d of approximately 30 nM and the K_d for the Class II RNA clone 27 was approximately 60 nM.

15 In order to identify the minimal sequence requirements for specific high affinity binding of the 76 nucleotide RNA which includes the variable 30N region flanked by 5' and 3' fixed sequence, 5' and 3' boundary experiments were performed (Example 12). For 20 5' boundary experiments the RNAs were 3' end labeled and hydrolyzed to give a pool of RNAs with varying 5' ends. For the 3' boundary experiments, the RNAs were 5' end-labeled and hydrolyzed to give a pool of RNAs with varying 3' ends. Minimal RNA sequence requirements were determined following RNA protein binding to nitrocellulose filters and identification of labeled RNA by gel electrophoresis (Example 12).

3' boundary experiments gave the boundaries for each of the 4 sequences shown in Table XIII. These boundaries were consistent at all protein concentrations. 5' boundary experiments gave the boundaries shown in Table XIII plus or minus 1 nucleotide, except for RNA 16 which gave a greater boundary with lower protein concentrations. Based on these boundary experiments, possible secondary structures of the thrombin ligands are shown in Figure

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7. RNAs corresponding to the smallest and largest hairpin of Class I clone 16 (SEQ ID NO:212) (24 and 39 nucleotides) and the hairpin of Class II clone 27 (SEQ ID NO:214) (33 nucleotides) were synthesized or transcribed for binding analysis (see Figure 7 and Example 13). Results show that the RNA 27 hairpin binds with affinity (K_d of about 60 nM) equal to that of the entire 72 nucleotide transcript with fixed and variable region (compare RNA 27 in Figure 8a with RNA 33R in Figure 8c). The K_d s for Class I clone 16 RNA hairpins on the other hand increased an order of magnitude from 30 nM to 200 nM.

15 Modifications in the 2'-ribose of pyrimidine residues of RNA molecules has been shown to increase stability of RNA (resistant to degradation by RNase) in serum by at least 1000 fold. 2'-NH₂ modified RNAs were prepared in Example 14. Binding experiments (Example 14) with the 2'-NH₂-CTP/UTP modified RNAs of Class I and Class II showed a significant drop in binding when compared to the unmodified RNA (Figure 9). Binding by the bulk 30N RNA, however, showed a slight increase in affinity when it was modified.

25 A ssDNA molecule with a 15 nucleotide consensus 5'-GGTGGTGGTGGTGG-3' (G15D) (SEQ ID NO:189) has been shown to bind human thrombin and inhibit fibrin-clot formation in vitro (Bock et al. (1992) Nature 355:564-565). The results of competition experiments for binding thrombin between G15D and the RNA hairpin ligands of this invention are shown in Figure 10 (see Example 15). In the first of these experiments (Experiment A) a ³²P-labeled G15D was used as the tracer with increasing concentrations of unlabeled RNA or unlabeled G15D. As expected, when the G15D was used to compete for its own binding, binding of labeled DNA was reduced to 50% at equimolar concentrations (1 μ M) of labeled and unlabeled

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competitor DNA. Both the Class I clone 16 synthetic RNAs 24 and 39, and the Class II clone 27 synthetic RNA 33 were able to compete for binding of G15D at this concentration. In the second experiment (Experiment B) the higher affinity Class II hairpin RNA 33 (K_d = 60 nM) was ³²P-labeled and used as the tracer with increasing concentrations of unlabeled RNA or unlabeled G15D DNA (K_d = 200 nM). In these experiments, the G15D was able to compete effectively with RNA 33 at higher concentrations than the RNA 33 competes itself (shift of binding to the right), which is what is expected when competing with a ligand with 3-4 fold higher affinity. The Class II hairpin RNA 33 (K_d = 60 nM) was competed only weakly by the Class I hairpin RNA 24 (K_d = 200 nM), suggesting that while there may be some overlap, the RNAs of these two classes may bind with high affinity to different yet adjacent or overlapping sites. Because both of these RNAs can compete for G15D binding, this DNA 15mer probably binds in the region of overlap between the Class I and Class II hairpins.

20 The ability of thrombin to cleave the [peptidyl] chromogenic substrate S2238 (H-D-Phe-Pip-Arg-pNltroaniline) (H-D-Phe-Pip-Arg-PNA) (Kabi Pharmacia) was measured in the presence and absence of the RNA ligands of this invention (Example 16). The hydrolysis by thrombin of the chromogenic substrate S-2238 (H-D-Phe-Pip-Arg-pNltroaniline) at the indicated thrombin and RNA concentration was measured photometrically at 405 nm (Table XIV). There was no inhibitory effect of RNA on this cleavage reaction at 10⁻⁴ M thrombin and 10⁻⁴ M RNA, 10⁻⁴ M thrombin and 10⁻⁴ M RNA or at 10⁻⁴ M thrombin and 10⁻⁴ M RNA. These results suggest that the RNA ligands do not bind in the catalytic site of the enzyme.

35 The ability of thrombin to catalyze clot formation by cleavage of fibrinogen to fibrin was

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measured in the presence and absence of RNA (Example 17). The conversion of fibrinogen to fibrin and resulting clot formation was measured by the tilt test in the presence and absence of the RNA ligand inhibitors described. When RNA was present at a concentration equal to the K_d (30 nM for Class I RNAs and 60 nM for Class II RNAs), which was in 5 to 10-fold excess of thrombin, clotting time was increased by 1.5-fold (Table XIV).

Representative ligands from Class I and Class II showed that these ligands had low affinity for ATIII at concentrations as high as 1 μ M (Example 18, Figure 11A). These ligands showed reduced affinity when compared with the bulk 30N3 RNA suggesting that there has been selection against non-specific binding. This is of particular importance because ATIII is an abundant plasma protein with high affinity for heparin, a polyanionic macromolecule. These results show that the evolution of a discrete structure present in the Class I and Class II RNAs is specific for thrombin binding and, despite its polyanionic composition, does not bind to a high affinity heparin binding protein. It is also important to note that these thrombin specific RNA ligands have no affinity for prothrombin (Example 18, Figure 11B), the inactive biochemical precursor to active thrombin, which circulates at high levels in the plasma ($\sim 1 \mu$ M).

Example 19 (Table XV) below describes the evolution of high affinity DNA ligands to thrombin utilizing SELEX. Candidate mixtures with 30 and 60 variable nucleotide regions were employed in separate experiments. The binding constants of several of the ligands to thrombin were obtained, and one of the ligands 60-18(38) (SEQ ID NO:279) was shown to inhibit coagulation by thrombin (Table XVI).

The nucleic acid ligands and nucleic acid ligand solutions to thrombin described herein are

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useful as pharmaceuticals and as part of gene therapy treatments. The ligands can also be useful for diagnostic purposes.

The concepts of vascular injury and thrombosis are important in the understanding of the pathogenesis of various vascular diseases, including the initiation and progression of atherosclerosis, the acute coronary syndromes, vein graft disease, and restenosis following coronary angioplasty.

The high-affinity thrombin binding RNA ligands of this invention may be expected to have various properties. These characteristics can be thought about within the context of the hirudin peptide inhibitors and the current understanding of thrombin structure and binding. Within this context and not being limited by theory, it is most likely that the RNA ligands are binding the highly basic anionic exosite. It is also likely that the RNA is not binding the catalytic site which has high specificity for the cationic arginine residue. One would expect the RNA ligands to behave in the same manner as the C-terminal hirudin peptides. As such, they would not strongly inhibit small peptidyl substrates, but would inhibit fibrinogen-clotting, protein C activation, platelet activation, and endothelial cell activation. Given that within the anionic exosite the fibrinogen-clotting and TN-binding activities are separable, it is possible that different high-affinity RNA ligands may inhibit these activities differentially. Moreover, one may select for one activity over another in order to generate a more potent anticoagulant than procogulant.

EXAMPLE 1. EXPERIMENTAL PROCEDURES.

Materials. BFGF was obtained from Bachem California (molecular weight 18,000 Da, 154 amino acids). Tissue culture grade heparin (average molecular weight 16,000 Da) was purchased from Sigma.

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Low molecular weight heparin (5,000 Da) was from Calbiochem. All other chemicals were at least reagent grade and were purchased from commercial sources.

SELEX. Evolution of High Affinity Ligands to bFGF. Essential features of the SELEX protocol have been described in detail in the SELEX Applications and in previous papers (Tuerk & Gold (1990) *Science* 249:505; Tuerk et al. (1992a) *Proc. Natl. Acad. Sci. USA* 89:6988; Tuerk et al. (1992b) in *Polymerase Chain Reaction* (Ferre, F. Mullis, K., Gibbs, R. & Ross, A., eds.) Birkhauser, NY). The SELEX protocol may be performed in generally the same manner for unmodified RNA selection as for selection with 2'-deoxy-2'-NH₂ pyrimidines as described in Example 4 below. Briefly, DNA templates for *in vitro* transcription (that contain a region of thirty random positions flanked by constant sequence regions) and the corresponding PCR primers were synthesized chemically (Operon). The random region was generated by utilizing an equimolar mixture of the four nucleotides during oligonucleotide synthesis. The two constant regions were designed to contain PCR primer annealing sites, a primer annealing site for cDNA synthesis, T7 RNA polymerase promoter region, and restriction enzyme sites that allow cloning into vectors (See Table I).

An initial pool of RNA molecules was prepared by *in vitro* transcription of about 200 picomoles (pmol) (10¹⁴ molecules) of the double stranded DNA template utilizing T7 RNA polymerase (New England Biolabs).

Transcription mixtures consisted of 100-300 nM template, 5 units/ μ l T7 RNA polymerase, 40 mM Tris-Cl buffer (pH 8.0) containing 12 mM MgCl₂, 5 mM DTT, 1 mM spermidine, 0.002% Triton X-100, and 4% PEG.

Transcription mixtures were incubated at 37 °C for 2-3 hours. These conditions typically resulted in transcriptional amplification of 10- to 100-fold.

Selections for high affinity RNA ligands to

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bFGF were done by incubating bFGF (10-100 pmol) with RNA (90-300 pmol) for 10 minutes at 37 °C in 50 μ l of phosphate buffered saline (PBS) (10.1 mM Na₂HPO₄, 1.8 mM KH₂PO₄, 137 mM NaCl, 2.7 mM KCl, pH 7.4), then separating the protein-RNA complexes from the unbound species by nitrocellulose filter partitioning (Tuerk & Gold (1990) *Science* 249:505). The selected RNA (which typically amounts to 0.3-8% of the total input RNA) was then extracted from the filters and reverse transcribed into cDNA by avian myeloblastosis virus reverse transcriptase (AMV RT, Life Sciences). Reverse

transcriptions were done at 48 °C (30 minutes) in 50 mM Tris buffer (pH 8.3), 60 mM NaCl, 6 mM Mg(OAc)₂, 10 mM DTT, and 1 unit/ μ l AMV RT. Amplification of the cDNA by PCR under standard conditions yielded sufficient amounts of double-stranded DNA for the next round of *in vitro* transcription.

Nitrocellulose Filter Binding Assay.

Oligonucleotides bound to proteins can be effectively separated from the unbound species by filtration through nitrocellulose membrane filters (Yarus & Berg (1970) *Anal. Biochem.* 25:450; Lowary & Uhlenbeck (1987) *Nucleic Acids Res.* 15:10483; Tuerk & Gold (1990) *Science* 249:505). Nitrocellulose filters (Millipore, 0.45 μ m pore size, type HA) were secured on a filter manifold and washed with 4-10 ml of buffer. Following incubations of ³²P-labeled RNA with serial dilutions of the protein (5-10 min) at 37 °C in buffer (PBS) containing 0.01% human serum albumin (HSN), the solutions were applied to the filters under gentle vacuum in 45 μ l aliquots and washed with 5 ml of PBS. The filters were then dried under an infrared lamp and counted in a scintillation counter.

Cloning and Sequencing. Individual members of the enriched pools were cloned into pUC18 vector and sequenced as described (Schneider et al. (1992) *J. Mol. Biol.* 228:862-869; Tuerk & Gold (1990) *supra*).

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EXAMPLE 2. SELEX EXPERIMENTS TARGETING bFGF.

Following the procedures described in Example 1 above, two SELEX experiments (Experiments A and B) targeting bFGF were initiated with separate pools of randomized unmodified RNA, each pool consisting of approximately 10^{14} molecules. The constant sequence regions that flank the randomized region, along with the corresponding primers, were different in each experiment. The two template/primer combinations used are shown in Table I.

Selections were conducted in PBS at 37 °C. The selection conducted in Experiment B was done in the presence of heparin (Sigma, molecular weight 5,000-32,000 Da, average molecular weight 16,000 Da) in the selection buffer at the molar ratio of 1/100 (heparin/bFGF). Heparin competes for binding of randomized RNA to bFGF. The amount of heparin used significantly reduced, but did not eliminate RNA binding to bFGF (data not shown). The rationale for using heparin was two-fold. First, heparin is known to induce a small conformational change in the protein and also stabilizes bFGF against thermal denaturation. Second, the apparent competitive nature of binding of heparin with randomized RNA to bFGF was expected to either increase the stringency of selection for the heparin binding site or direct the binding of RNA ligands to alternative site(s).

Significant improvement in affinity of RNA ligands to bFGF was observed in Experiment A after ten rounds, and in Experiment B after thirteen rounds. Sequencing of these enriched pools of RNA ligands revealed a definite departure from randomness which indicated that the number of different molecules remaining in the pool was substantially reduced. Individual members of the enriched pools were then cloned into pUC18 vector and sequenced as described in Example 1.

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49 clones were sequenced from Experiment A, and 37 clones from Experiment B. From the total of 86 sequences, 71 were unique. Two distinct families could be identified based on overlapping regions of sequence homology (Tables II and III, XVII and XVIII). A number of sequences with no obvious homology to members of either of the two families were also present, as expected (Irvine et al. (1991) J. Mol. Biol. 222:739), and are shown in Table IV.

The consensus sequence from Family 1 ligands (Table II) is defined by a contiguous stretch of 9 bases, CUAACCAAG (SEQ ID NO:7). This suggests a minimal structure consisting of a 4-5 nucleotide loop that includes the strongly conserved AAC sequence and a bulged stem (Figure 4 and Table VI). The consensus sequence for Family 2 ligands (Table III) is more extended and contains less conserved regions, RGGHACGYWNNGDCAANNACAC (SEQ ID NO:23). Here, most of the strongly conserved positions are accommodated in a larger (19-21 nucleotide) loop (Figure 4 and Table VII). Additional structure within the loop is possible.

The existence of two distinct sequence families in the enriched pools of RNA suggest that there are two convergent solutions for high-affinity binding to bFGF. SELEX Experiment A contributed members to both sequence families (Table II). All of the sequences from the SELEX Experiment B (selected in the presence of heparin), on the other hand, belong either to Family 2 (Table III) or to the "other sequences" family (Table IV), but none were found in Family 1. This is surprising in view of the fact that bFGF was present in a molar excess of 100-fold over heparin during selections. The effective molar excess of bFGF over heparin, however, was probably much smaller. Average molecular weight of heparin used in selections was 16,000 Da. Since each sugar unit weighs

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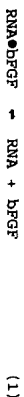
320 Da and at least eight sugar units are required for high-affinity binding to bPGF, six molecules of bPGF, on average, can bind to a molecule of heparin. This reduces the molar ratio of heparin to bPGF to 1:16. In practice, this amount of heparin is sufficient to reduce the observed affinity of the unselected RNA pool for bPGF by a factor of five (data not shown). The observed exclusion of an entire ligand family by the presence of a relatively small amount of heparin in the selection buffer may be a consequence of a conformational change in the protein induced by heparin. Because of the relative amounts of heparin and bPGF that were used in selections, this model may require that the heparin-induced conformation persist after the protein-heparin complex has dissociated, and that the lifetime of this conformer is long enough to permit equilibration with the RNA ligands.

Family 2 sequences are comprised of clones derived from both SELEX experiments. This suggests that the flanking constant regions typically play a relatively minor role in determining the affinity of these ligands and supports the premise that the consensus sequence in this family is the principal determinant of high-affinity binding to bPGF.

EXAMPLE 3. DETERMINATION OF BINDING AFFINITIES FOR bPGF.

Equilibrium Dissociation Constants.

In the simplest case, equilibrium binding of RNA to bPGF can be described by equation 1:



The fraction of bound RNA (q) is related to the concentration of free protein, $[P]$ (equation 2):

$$q = f[P]/([P] + K_d) \quad (2)$$

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where K_d is the equilibrium dissociation constant and f reflects the efficiency of retention of the protein-RNA complexes on nitrocellulose filters. Mean value of f for bPGF was 0.82.

In order to eliminate higher order structures, all RNA solutions were heated to 90 °C in PBS for 2-3 minutes and cooled on ice prior to incubation with protein. Only single bands for all RNA clones were detected on non-denaturing polyacrylamide gels following this treatment.

Relative binding affinity of individual ligands to bPGF cannot be predicted from sequence information. Unique sequence clones were therefore screened for their ability to bind to bPGF by measuring the fraction of radiolabeled RNA bound to nitrocellulose filters following incubation with 4 and 40 nM protein. This screening method was sufficiently accurate to allow several clones to be identified that had dissociation constants in the nanomolar range. Binding of these select clones was then analyzed in more detail.

High-affinity RNA ligands for bPGF were found in both sequence families (Tables VI and VII). The affinity of clones that did not belong to either family was generally lower (data not shown).

The original, unselected RNA pools bound to bPGF with 300 nM (set A) and 560 nM (set B) affinities (Figure 1). SELEX therefore allowed the isolation of ligands with at least 2 orders of magnitude better affinity for bPGF.

In order to address the question of specificity, a representative set of high-affinity ligands for bPGF (5A (SEQ ID NO:9) and 7A (SEQ ID NO:10) from Family 1, 12A (SEQ ID NO:25) and 26A (SEQ ID NO:26) from Family 2) were tested for binding to four other heparin-binding proteins. It was found that the affinity of these ligands for acidic PGF, thrombin,

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of biphasic binding see Jellinek et al. (1993) Proc. Natl. Acad. Sci. USA 20:11227-11231). Binding of ligand 58A-t to bFGF is also biphasic ($K_{d1} = 1.8 \text{ nM}$, $\chi^2 = 0.5$, $K_{d2} = 180 \text{ nM}$). Binding of ligand 34B-t is monophasic ($K_{d1} = 3 \text{ nM}$).

The ability to inhibit the binding of ^{125}I -bFGF to high and low-affinity cell-surface receptors was examined (Figure 6). Experiments were conducted as described in Moscatelli (1987) J. Cell. Physiol.

131:123 using confluent cultures of baby hamster kidney cells. Specific activity of bFGF was 915 cpm/fmol. Each data point represents the average of two experiments.

Several high-affinity ligands were found to inhibit binding of bFGF to its cell-surface receptors, with truncated versions of ligand 21A being the most effective inhibitors (Figure 6B). Random RNA was ineffective in this concentration range (up to $1 \mu\text{M}$).

20 EXAMPLE 5. RNA LIGAND INHIBITION OF bFGF RECEPTOR BINDING.

The same four high-affinity RNA ligands (5A (SEQ ID NO:9) and 7A (SEQ ID NO:10) from Family 1, 12A (SEQ ID NO:25) and 26A (SEQ ID NO:26) from Family 2) described in Example 3 were also tested for their ability to inhibit binding of bFGF to the low- and the high-affinity cell-surface receptors. Additionally, modified RNA ligands 21A (SEQ ID NO:104), 38B (SEQ ID NO:114) and Random RNAs were tested.

30 Receptor Binding Studies. bFGF was labeled with ^{125}I by the Iodo-Gen (Pierce) procedure as described by Moscatelli (1987) J. Cell. Physiol. 131:123. Confluent baby hamster kidney (BHK) cells were washed extensively with PBS and then incubated for 2 hours at 4°C with αMEM medium containing 10 ng/ml ^{125}I -bFGF in PBS, 0.1% HSA, 1 unit/ml RNasein, and serial dilutions of high-affinity RNA. In a separate

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experiment it was established that the RNA is not significantly degraded under these conditions. The amount of ^{125}I -bFGF bound to the low- and the high-affinity receptor sites was determined as described by Moscatelli (1987) supra.

All four ligands competed for the low-affinity receptor sites while the unselected (random) RNAs did not (Figure 2A). The concentration of RNA required to effect half-displacement of bFGF from the low-affinity receptor was 5-20 nM for ligands 5A, 7A and 26A, and $>100 \text{ nM}$ for ligand 12A. Half-displacement from the high-affinity sites is observed at the concentration of RNA near $1 \mu\text{M}$ for ligands 5A, 7A and 26A, and $>1 \mu\text{M}$ for ligand 12A (Figure 2B). Again, random RNAs did not compete for the high-affinity receptor. The observed difference in concentration of RNA required to displace bFGF from the low- and high-affinity receptors is expected as a reflection of the difference in affinity of the two receptor classes for bFGF ($2\text{-}10 \text{ nM}$ for the low-affinity sites and $10\text{-}100 \text{ pM}$ for the high-affinity sites).

Binding curves for modified RNA ligands 21A (SEQ ID NO:104), 38B (SEQ ID NO:114) and random RNAs were determined (Figure 5). RNA concentrations were determined from their absorbance reading at 260 nm and were typically less than 100 pM . Binding reactions were conducted at 37°C in phosphate buffered saline containing 0.01% human serum albumin and 1 mM DTT. Heparin competitively displaced RNA ligands from both sequence families (Figure 3), although higher concentrations of heparin were required to displace members of Family 2 from bFGF.

The selective advantage obtained through the SELEX procedure is based on affinity to bFGF. RNA ligands can in principle bind to any site on the protein, and it is therefore important to examine the activity of the ligands in an appropriate functional

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assay. The relevant functional experiment for the selected high-affinity ligands is testing their ability to inhibit binding of bFGF to its cell-surface receptors since this is how bFGF exerts its biological activity. The fact that several representative high-affinity RNA ligands inhibited binding of bFGF to both receptor classes (in accord with their relative binding affinities) suggests that these ligands bind at or near the receptor binding site(s). Further support for this notion comes from the observation that heparin competes for binding of these ligands to bFGF. High affinity ligands from Family 1 and Family 2 may bind to different sites on bFGF. This invention includes covalently connecting components from the two ligand families into a single, more potent inhibitor of bFGF.

EXAMPLE 6. *IN VIVO* INHIBITION OF bFGF ACTIVITY WITH 2'-NH₂-MODIFIED RNA LIGANDS.

The potential *in vivo* activity of the bFGF antagonist oligonucleotide 2'-NH₂ ligand 21A (SEQ ID NO:104) was evaluated in the rat corneal angiogenesis assay. The basic approach for this assay was originally developed and reported by Gimbrone et al. (1974) JNCI 52:413-419 using rabbit corneas for implantation of tumor cells or tumor cell extracts in polyacrylamide gel. The technique was later refined by Langer and Folkman (1976) Nature 263:797 to utilize a less irritating polymer, hydroxyethylmethacrylate (Hydron). The corneal implantation method for assessing angiogenic activity associated with cell extracts or growth factors suspended in Hydron has been used in guinea pigs by Poverini et al. (1977) Nature 269:804 and more recently in rats by Koch et al. (1992) Science 258:1798.

The corneal angiogenesis assay used herein is a modification of the techniques described in the above references. The assay is conducted in rat corneas;

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however, the implantation method is different in that the corneal pocket is made using small scissors instead of a spatula for the blunt dissection of the corneal stroma. Additionally, Hydron could not be used as the carrier substance for bFGF because the protein was denatured by the high concentration of ethanol and/or the polymerization reaction. Other carriers were studied and it was determined that nitrocellulose filter material (Millipore) was the most suitable medium for implantation since it readily absorbs the protein, is not denaturing to proteins, and is not proinflammatory or irritating to the corneal stroma.

The basic design of the first *in vivo* assay was to compare the potential angiogenic effects of (1) untreated nitrocellulose, (2) nitrocellulose soaked in oligonucleotide 2'-NH₂ ligand 21A, (3) nitrocellulose soaked in bFGF, and (4) nitrocellulose soaked in a solution of ligand 21A and bFGF combined.

The disks to be implanted were punched out of a standard Millipore nitrocellulose filter using a punch made from a 16 gauge hypodermic needle. The diameter of the implanted disks was approximately 1mm. Prior to implantation the disks were soaked in a given test solution for at least one hour to ensure saturation. The four solutions in this experiment were (1) Ringer's physiologic salt solution, (2) RNA ligand 21A in 10% PBS/90% water, (3) bFGF in Ringer's solution, and (4) 1:1 mixture of ligand 21A and bFGF.

The respective soaked disks were implanted into the corneal stroma of three rats for each treatment group. Both eyes of each rat received the same treatment so that there were six test eyes in each test group. The test solutions were handled using sterile technique. The animals were anesthetized with a general anesthetic mixture containing acepromazine, ketamine, and xylazine. The corneal surgery, which involved making an incision through the corneal

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epithelium into the underlying stroma with subsequent dissection of a pocket in the stroma, was conducted under a stereomicroscope. The surgical site was cleaned with a dilute solution of organic iodine. A single dose of ophthalmic antibiotic was administered post-surgically.

Following implantation of the disks, the animals were returned to their cages where they were maintained under standard husbandry conditions until their eyes were examined stereomicroscopically on post-surgical days seven and fourteen. The eyes were evaluated for amount of corneal cloudiness around the implant and for amount of vascular ingrowth into the normally avascular cornea. The scoring system used for quantitation of vascular ingrowth was based on degrees of vascularization around the circumference of the cornea (potential total = 360°) multiplied by the extent of vascular ingrowth toward the implant (1 = no growth; 2 = ingrowth 1/3 of distance to implant; 3 = ingrowth 2/3 of distance to implant; 4 = ingrowth to implant; 5 = ingrowth into and around implant). The mean score of the eyes in each group was then determined. The minimum score of 360 (360 x 1) is normal while the maximum possible score with extensive vascular ingrowth into the implant is 1800 (360 x 5). The results are shown in Table X.

The results from this preliminary experiment provide two important findings for this ligand. First, although the ligand did not prevent the bFGF stimulated ingrowth of vessels into the cornea (Group IV vs. Group III), it did diminish the amount of vascular ingrowth, as well as, the amount of corneal cloudiness observed microscopically at both seven and fourteen days following implantation. Second, the introduction of the oligonucleotide alone (Group II) into the cornea did not result in any adverse effects such as irritation, inflammation, or angiogenesis. These

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findings suggest that the oligonucleotide has the desired antagonistic effect for bFGF and that it is biocompatible when administered in vivo at relatively high local concentration (60 μ M).

EXAMPLE 7. ENDOTHELIAL CELL MIGRATION ASSAY.

The effect of minimal 2'-amino pyrimidine RNA ligand on endothelial cell motility was examined by measuring the migration of endothelial cells into a denuded area (Sato, Y. and Rifkin, D. B. (1989) J. Cell Biol. 102:309-315). Confluent monolayers of bovine aortic endothelial (BAE) cells were scraped with a razor blade to create a denuded area on the culture dish. The number of endothelial cells that moved from the edge of the wound into the denuded area in the presence of varying concentrations of oligonucleotide ligands was determined after 8 hours. The movement of BAEs under untreated conditions is dependent on endogenous bFGF and can be inhibited by addition of neutralizing antibodies to bFGF. Ligand 21A-ts (5'-GGUGUGGAGAGACGCGGUGUGUC-3' (SEQ ID NO:444) inhibited BAE migration in a dose dependent manner at concentrations greater than 50 nM (Ligand 21A-ts is a chemically synthesized analogue of 2'-NH₂ ligand 21A-c (SEQ ID NO:186) in which the terminal 2'-amino cytidine has been converted to deoxycytidine. This substitution does not affect high affinity binding to bFGF). The control ligand deoxy(21A-ts) (all deoxy sequence equivalent of 21A-c: 5'-GGUGUGGAGAGACGCGGUGUC-3' (SEQ ID NO:445)) did not inhibit BAE migration at the same concentrations. In fact a moderate stimulation of migration was observed. The extent of inhibition at high RNA ligand concentrations varied significantly between experiments ranging from almost 100% to < 50% inhibition (data not shown). This is probably related in part to variable expression of other motility-inducing growth factors by BAE cells between

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experiments as well as subtle differences in the state of the cells at the time of wounding. Importantly, the total amount of motility that could be inhibited by 21A-ts at high concentrations was comparable in all experiments to the effect of 100 µg/ml neutralizing bFGF antibody. This concentration of antibody is generally sufficient to inhibit all of the bFGF-dependent migration of endothelial cells. In a separate experiment we established that the oligonucleotides used in this experiment are not appreciably degraded over the duration of this experiment (6 hr) in a variety of cell culture conditions (data not shown).

15 EXAMPLE 8. bFGF DNA LIGANDS.

The SELEX protocol was performed in a manner similar to that described in Example 1 to obtain single stranded DNA (ssDNA) ligands to bFGF.

Here, SELEX is performed with single stranded DNA (ssDNA) starting with the three separate sets of synthetic DNA oligonucleotide templates and primers (Experiments 1-3) shown in Table XIX. These experiments are further split into two different methods of ssDNA partitioning from double stranded DNA (dsDNA).

Briefly, in Experiment 1 a population of synthetic DNA oligonucleotides (40N2, SEQ ID NO:322) containing 40 random nucleotides flanked by invariant primer annealing sites was amplified by the Polymerase Chain Reaction (PCR) using oligos 3p2 (SEQ ID NO:323) and ³²P end labeled 5p2 (SEQ ID NO:321) as primers. Oligo 3p2 has three biotin phosphoramidites covalently attached to its 5' terminus during synthesis. In order to generate the ssDNA library from the PCR products, oligo 40N2 was separated from its complement. This was achieved by incubating the PCR reaction in the presence of a 10 fold molar excess of Pierce streptavidin over the biotinylated complement strand. The non-biotinylated ssDNA 40N2 was

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then purified away from the streptavidin labeled complement strand on a 12% denaturing gel. The ssDNA was eluted from the gel and precipitated, and the ssDNA library used for the selections.

Experiments 2 and 3 used two different populations of synthetic DNA oligonucleotides, oligos 40NBH1 (SEQ ID NO:325), and 30N7.1PS (SEQ ID NO:326), containing 40 and 30 random nucleotides respectively flanked by invariant primer annealing sites. The DNA pools were amplified by the Polymerase Chain Reaction (PCR) using oligos 3pBH1 (SEQ ID NO:326) and 5pBH1 (SEQ ID NO:324) in Experiment 2 and oligos 3p7.1PS (SEQ ID NO:329) and 5p7.1PS (SEQ ID NO:327) in Experiment 3 as primers for the appropriate invariant regions on template molecules. Oligos 3pBH1 and 3p7.1PS had two biotin molecules and two additional A nucleotides covalently attached via standard phosphoramidite coupling to their 5' terminus during synthesis. The non-biotinylated primer was end labeled with ³²P. The radiolabeled non-biotinylated single-stranded PCR products were size-purified away from the biotinylated strand on 8% denaturing acrylamide gels to give single stranded degenerate DNA pools. DNA templates for PCR and the corresponding primers were all synthesized chemically (Operon). The random region was generated by utilizing an equimolar mixture of the four nucleotides during oligonucleotide synthesis.

Using the above methods, three pools of ssDNA oligonucleotides were created that contain internal random regions. From each starting ligand pool approximately 10¹⁴ molecules of DNA was incubated with bFGF at an excess of DNA to target. Oligonucleotides bound to bFGF can be effectively selected from the unbound species by filtration through nitrocellulose membrane filters. The nitrocellulose filters (Millipore, 0.45 µm pore size, type HA) were secured on a

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filter manifold pre-washed with PBS, the incubation mix washed through and the filter washed with 0.5 M Urea and PBS buffer to remove non-specific DNA from the filter.

The selected DNA (which typically amounts to 1-5% of the total input DNA) was then extracted from the filters. Amplification of the selected ssDNA was performed by PCR under standard conditions yielded sufficient amounts of double-stranded DNA for the next round of selection.

Selections were performed at a large molar excess of ssDNA over protein to promote competition among DNA ligands for the limited number of available target binding sites. The percent of target-dependent DNA retention was minimized for each selection to ensure maximum enrichment of the library for target binders; however, to avoid propagation of members with high affinity for nitrocellulose, selections in which target-free (background) retention was greater than 10% of target-dependent retention were repeated. Target-free selections were performed to measure and correct for background binding levels. The fraction of total DNA retained by the filters was calculated by measuring radiation without fluor in a scintillation counter. The affinity of the pool for bFGF was measured periodically throughout each of the three selection experiments. As the affinity of the population for bFGF increased, the concentrations of ligand and target were reduced accordingly, while the ligand was maintained at an excess concentration, to increase selection stringency. Table XX shows a typical SELEX progression as was seen in Experiment 3. The nucleic acid concentration was maintained at a five fold excess to the bFGF concentration, in all but the first round. Attempts were made to maintain a level of background that was 10 fold lower than the percent bound. The binding affinity was

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tested after round 0, 8, 10 and 11 to follow the progression.

Cloning and Sequencing.

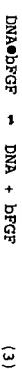
As indicated in Table XX, significant improvement in affinity of DNA ligands to bFGF was observed in each of the three experiments after ten rounds of selection. Individual members of these enriched pools were then cloned into Stratagene PCR Script SK (+) or pUC18 vector and sequenced. Sequencing of the isolates resulted in 78 individual sequences. Experiment 1 resulted in 36 clones, Experiment 2 resulted in 29, and Experiment 3 resulted in 43. As shown in Table XXI, five distinct families could be identified based on 40% or better overlap in sequence homology. A number of sequences with no obvious homology to members of the five families were also present. These sequences are listed as orphans.

Each family is further divided into the three different SELEX experiments. The consensus sequence for Family 1 ligands is defined by a contiguous stretch of 9 bases, GGCGCTWGTCAAN (SEQ ID NO:340) where the two N positions are covariant combination of all four bases. This suggests a minimal structure consisting of a 4 nucleotide loop that includes the strongly conserved GCNA sequence. The loop is closed by the formation of a stem containing a T-A basepair and the covariant base pair position.

Determination of Binding Affinities for bFGF.

Equilibrium Dissociation Constants.

In the simplest case, equilibrium binding of DNA to bFGF can be described by equation 3:



The fraction of bound DNA (q) is related to the concentration of free protein, $[P]$. Where the

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concentration of free protein approximates the concentration of total protein (equation 4):

$$q = f[P] / ([P] + K_d) \quad (4)$$

where K_d is the equilibrium dissociation constant and f reflects the efficiency of retention of the protein-DNA complexes on nitrocellulose filters. Mean value of f for bFGF was determined to be 0.82.

In order to eliminate higher order structures, all DNA solutions were heated to 90 °C in PBS for 2-3 minutes and cooled on ice prior to incubation with protein.

Relative binding affinity of individual ligands to bFGF cannot be predicted from sequence information. The majority of sequence isolates were therefore screened for their ability to bind to bFGF by measuring the fraction of radiolabeled DNA bound to nitrocellulose filters following incubation with 1 nM protein. This screening method was sufficient to discern those isolates with superior binding to bFGF. Binding of these select isolates was then analyzed in more detail.

High-affinity DNA ligands for bFGF were found in all five sequence families (see (*) in Table XII), but the DNAs with the lowest K_d values (i.e. ligands with highest affinity) were found in Family 1.

The isolates tested for affinity for bFGF are listed in Table XXII.

Truncation Analysis.

Removal of nucleotides non-essential for binding was performed on selected ligands with high affinity for bFGF, K_d s below 1 nM. Those ligands are M225, M19, m234, M235, and D12 (SEQ ID NOS:359, 353, 387, 360, 332). The minimum size of the region necessary for binding was determined to be 35 bases for M225, M19 and D12 (See Truncations, Table XXI M225t3 (SEQ ID NO:364), M19t2 (SEQ

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ID NO:365), D12t2 (SEQ ID NO:341)). The ligand with the smallest essential sequence, m234, was isolated from Family 2, Experiment 3 and contains 24 nucleotides (m234t2 (SEQ ID NO:391)). The truncated ligands were tested for binding to bFGF. After truncation, ligands M225t3, M19t2, D12t2, M235t2, and m234t2 have K_d values of 0.7 nM, 1 nM, 1 nM, 1 nM, and 6 nM respectively (Table XXII). All five of the truncated molecules lost some of their affinity for bFGF in comparison to the full length ligands. The binding affinity is regained when an additional G-C base pair is added to the blunt end stem of M225t3. This molecule is termed M225t3GC (SEQ ID NO:443). The binding of M225t3GC is 0.2 nM compared to 0.7 nM for M225t3 without the additional base pair (Table XXII).

Receptor Binding Studies.

The truncated molecules were tested for their ability to inhibit binding of bFGF to its low- and the high-affinity cell-surface receptors.

bFGF labeled with 125 I was purchased from Amersham. Confluent baby hamster kidney (BHK) cells were washed extensively with PBS and then incubated for 2 hours at 4 °C with a MEM medium containing 10 ng/ml 125 I-bFGF in PBS, 0.1% HSA, 1 unit/ml RNasin, and serial dilutions of high-affinity DNA. The amount of 125 I-bFGF bound to the low- and the high-affinity receptor sites was determined as described by Moscatelli (1987) BUDXA.

All five ligands competed for the low-affinity and high-affinity receptor sites while the unselected (random) RNAs did not. All five ligands show inhibition in the nanomolar range.

Specificity.

Ligand M225t3 (SEQ ID NO:364) the truncated version of the full length isolate M225 (SEQ ID NO:359) was chosen as the preferred ligand for further study. This

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was based on its sub-nanomolar binding (Table XXII), its T_m of 68 °C which indicates a stable structure, possibly containing a G-C rich stem, and a 35 base truncation. The sequence of M25tc3 results in a DNA that folds into a structure containing a 6 base G-C stem terminating in a blunt end. Using the covariant site in the conserved region a GYAA loop can be proposed in the consensus region:

In order to address the question of specificity, ligand M25tc3 was tested for binding to vascular endothelial growth factor and human chorionic gonadotropin, both heparin-binding proteins. It was found that the affinity of M25tc3 for these proteins was relatively weak ($K_d > 0.2 \mu M$).

EXAMPLE 9. CONFIGURATION OF PEG LIGAND TO PEG.

In an effort to determine whether enhanced circulation time could be obtained by conjugating the bFGF to a high molecular weight species, such as PEG, M25tc3 DNA was synthesized with a 3' carbon linker terminating in a primary NH₂ group. The modified DNA was then reacted with an excess of an N-hydroxysuccinimideyl active ester of PEG 3400. The product was isolated as a slower running band on a gel. It was then labeled and a binding assay performed. The PEG modified M25tc3 binds with a similar affinity to bFGF as the non modified ligand. The PEG modified M25tc3 binds with the a K_d of 1 nM.

EXAMPLE 10. EVOLUTION OF HIGH AFFINITY RNA LIGANDS TO THROMBIN.

High affinity RNA ligands for thrombin were isolated by SELEX, as generally described in Example 1. Briefly, random RNA molecules used for the initial candidate mixture were generated by *in vitro* transcription from a 102 nucleotide double-stranded DNA template containing a

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random cassette 30 nucleotides (30N) long. A population of 10¹¹ 30N DNA templates were created by PCR, using a 5' primer containing the T7 promoter for *in vitro* transcription, and restriction sites in both the 5' and 3' primers for cloning. SELEX was performed with an RNA candidate mixture containing the following 76 nucleotide sequences: 5'-AGAGCCGCG CGACGAGCTG(30N)GAGCUNAA CAGCUGUGCAGCGAG-3' (SEQ ID NO:320).

The RNA concentration for each round of SELEX was approximately 2-4 X 10⁷ M and concentrations of thrombin (Sigma, 1000 units) went from 1.0 X 10⁻⁴ in the 1st round to 4.8 X 10⁻⁷ in rounds 2 and 3 and 2.4 X 10⁻⁷ in rounds 4-12. The binding buffer for the RNA and protein was 100 mM NaCl, 50 mM Tris-Cl, pH 7.7, 1 mM DTT, and 1 mM MgCl₂. Binding was for 5 minutes at 37°C in a total volume of 100 μ l in rounds 1-7 and 200 μ l in rounds 8-12. Each binding reaction was filtered through a pre-wetted (with 50 mM Tris-Cl, pH 7.7) nitrocellulose filter (2.5 cm Millipore, 0.45 μ m) in a Millipore filter binding apparatus, and immediately rinsed with 5 ml of the same buffer. The RNA was eluted from the filters in 400 μ l phenol (equilibrated with 0.1 M NaOAc pH 5.2), 200 μ l freshly prepared 7 M urea as described (Therk et al. (1990) J. Mol. Biol. 213:749-761. The RNA was precipitated with 20 μ g tRNA, and was used as a template for cDNA synthesis, followed by PCR and *in vitro* transcription to prepare RNA for the subsequent round. The RNA was radio-labeled with ³²P-ATP in rounds 1-8 so that binding could be monitored. In order to expedite the time for each round of SELEX, the RNA was not labeled for rounds 9-12. RNA was prefiltered through nitrocellulose filters (1.3 cm Millipore, 0.45 μ m) before the 3rd, 4th, 5th, 8th, 11th, and 12th rounds to eliminate selection for any nonspecific nitrocellulose binding.

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Binding curves were performed after the 5th, 8th, and 12th rounds to estimate changes in K_d of the bulk RNA (data not shown). These experiments were done in protein excess at concentrations from 1.2×10^{-4} to 2.4×10^{-9} M at a final RNA concentration of 2×10^{-9} M. The RNA for these binding curves was labeled to high specific activity with γ -ATP or γ -UTP. Binding to nitrocellulose filters was as described for the rounds of SELEX, except that the filter bound RNA was dried and counted directly on the filters.

EXAMPLE 11. CLONING AND RNA SEQUENCING.

RNA recovered from the 12th round of SELEX was reverse transcribed into DNA with AMV reverse transcriptase (Life Sciences, Inc.) and the resulting DNA was amplified by PCR using the γ -P 5' end-labeled 3' complementary PCR primer. Digestion at restriction enzyme sites in the 5' and 3' fixed regions were used to remove the 30N region which was subsequently ligated into the complementary sites in the *E. coli* cloning vector pUC18. Ligated plasmid DNA was transformed into JM103 cells and screened by blue/white colony formation. Colonies containing unique sequences were grown up and miniprep DNA was prepared. Double-stranded plasmid DNA was used for dideoxy sequencing with the Sequenase kit version 2.0 and 35 S-dATP (Amersham). Twenty eight individual clones were sequenced (see Table XII). The ligands were grouped into two classes based upon primary sequence homology.

EXAMPLE 12. DETERMINATION OF 5' AND 3' BOUNDARIES.

In order to identify the minimal sequence requirements for high affinity binding, 5' and 3' boundary experiments were performed with end-labeled RNA. Prior to end-labeling, RNA transcribed with T7 polymerase

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was gel purified by UV shadowing. The RNA was 5' end-labeled by dephosphorylating the 5' end with alkaline phosphatase 1 unit, for 30 minutes at 37 °C. Alkaline phosphatase activity was destroyed by phenol:chloroform extraction. RNA was subsequently end-labeled with γ -ATP in a reaction with polynucleotide kinase for 30 minutes at 37 °C.

RNA was 3' end-labeled with (5'- γ -ATP)pCp and RNA ligase, for 30 minutes at 37 °C. 5' and 3' end-labeled RNAs were gel band purified on an 8%, 8 M urea, polyacrylamide gel.

2 pmole RNA 3' or 5' end-labeled for the 5' or 3' boundary experiments, respectively were hydrolyzed in 50 mM Na_2CO_3 (pH 9.0) and 1 mM EDTA in a 10 μ l reaction for 10 minutes at 90 °C. The reaction was stopped by adding 1/5 volume 3 M NaOAc (pH 5.2), and freezing at -20 °C. Binding reactions were done at 3 protein concentrations, 40 nM, 10 nM and 2.5 nM, in 3 volumes (100 μ l, 400 μ l, and 1600 μ l, such that the amount of protein was kept constant) containing 1X binding buffer and 2 pmoles RNA. Reactions were incubated for 10 minutes at 37°C, filtered through a pre-wet nitrocellulose membrane, and rinsed with 5 ml wash buffer. The RNA was eluted from the filters by dipping the filter and shaking it in 200 μ l 7 M urea and 400 μ l phenol (pH 8.0) for 15 minutes at 20 °C. After adding 200 μ l H_2O , the phases were separated and the aqueous phase extracted once with chloroform. The RNA was precipitated with 1/5 volume 3 M NaOAc, 20 μ g carrier tRNA, and 2.5 volumes ethanol. The pellet was washed once with 70% ethanol, dried, and resuspended in 5 μ l H_2O and 5 μ l formamide loading dye. The remainder of the alkaline hydrolysis reaction was diluted 1:10 and an equal volume of loading dye was added.

To locate where on the sequence ladder the boundary existed, an RNase T1 digest of the ligand was

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electrophoresed alongside the alkaline hydrolysis reaction and binding reactions. The digest was done in a 10 μ l reaction containing 500 fmol of end-labeled RNA and 10 units RNase T1 in 7 M urea, 20 mM sodium citrate (pH 5.0) and 1 mM EDTA. The RNA was incubated for 10 minutes at 50 °C without enzyme and then another 10 minutes after adding enzyme. The reaction was slowed by adding 10 μ l loading dyes and incubating at 4 °C. Immediately after digestion, 5 μ l of each of the digest, hydrolysis, and 3 binding reactions were electrophoresed on a 12% sequencing gel. The boundary experiments gave the boundaries depicted in Table XIII. Based upon these boundaries, possible secondary structures of the thrombin ligand are shown in Figure 7.

EXAMPLE 13. SYNTHESIS OF RNA.

RNA molecules corresponding to lower limits of nucleotide sequence required for high affinity binding to thrombin as determined by the boundary experiments (Table XIII and Figure 7) were synthesized on an Applied Biosystems 394 DNA/RNA Synthesizer. These RNA molecules include the Class I clone 16 (SEQ ID NO:212) hairpin structures of 24 nucleotides (24R) and 39 nucleotides (39R) and the Class II clone 27 (SEQ ID NO:214) hairpin of 33 nucleotides (33R).

EXAMPLE 14. IN VITRO TRANSCRIPTION AND BINDING OF 2'-NH₂ MODIFIED AND UNMODIFIED RNA LIGANDS.

Four DNA plasmids with unique 30N sequences were chosen for in vitro transcription of selected unmodified and 2'-NH₂ modified RNA ligands from Class I and Class II. 2'-NH₂ modified RNA was transcribed directly from the pUC18 plasmid miniprep dsDNA template with T7 RNA polymerase in a reaction containing ATP, GTP, 2'-NH₂-UTP and 2'-NH₂-CTP. Unmodified RNAs were transcribed in a

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mixture containing ATP, GTP, UTP, and CTP. For ³²P-labeled RNA, ³²P-ATP was included in the reaction. ³²P-labeled RNA was transcribed with conventional nucleotides, as well as, with the 2'-NH₂ derivatives of CTP and UTP. Binding curves with these individual RNAs were established using the binding buffer and thrombin (1000 units, Sigma) concentrations from 1.0 x 10⁻⁴ to 1.0 x 10⁻⁶ M. Human α thrombin (Enzyme Research Laboratories, ERL) was also used to determine binding affinities of RNA at concentrations from 1.0 x 10⁻⁴ to 1.0 x 10⁻⁶ M.

The 2'-NH₂-CTP/UTP modified RNAs of Class I and Class II showed a significant drop in binding when compared to the unmodified RNA (Figure 9). Binding by the bulk 30N RNA, however, showed a slight increase in affinity when it was modified.

Binding of the 5' end-labeled single stranded 15mer DNA 5'-GGTTGGTGTGTTGG-3' (G15D) (SEQ ID NO:189) described by Bock et al. (1992) Nature 355:564-565, was determined under the binding conditions described herein with ERL thrombin and compared to binding by the radiolabeled RNA hairpin structures described above. (see Figure 8C).

EXAMPLE 15. COMPETITION EXPERIMENTS.

To determine whether the RNA ligands described can compete for binding of the DNA 15mer G15D to thrombin, equimolar concentrations (1 μ M) of thrombin and the 5' end labeled DNA 15mer G15D were incubated under filter binding conditions (Kd of approximately 200 nM) in the presence and absence of 'cold' unlabeled RNA or DNA ligand at varying concentrations from 10 nM to 1 μ M. In the absence of competition, RNA binding was 30%. The protein was added last so competition for binding could occur. The RNA ligands tested for competition were the

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Class I clone 16 (SEQ ID NO:212) synthetic RNAs 24mer (24R) and 39mer hairpins (39R) and the Class II 27 (SEQ ID NO:214) synthetic RNA 33mer (33R). Results are expressed as the relative fraction of G15D bound (G15 with competitor/G15 without competitor) versus the concentration of cold competitor.

To determine whether Class I RNAs can compete for binding with Class II RNAs and to confirm the competition with the G15D RNA, equimolar concentrations (300 nM) of thrombin and the 5' end-labelled Class II RNA 33 hairpin were incubated under filter binding conditions in the presence or absence of 'cold' unlabelled RNA 24 or DNA G15D at varying concentrations from 100 nM to 32 μ M. Results are expressed as the relative fraction of RNA 33 bound (RNA 33 with competitor/RNA 33 without competitor) versus the concentration of cold competitor (Figure 10).

EXAMPLE 16. CHROMOGENIC ASSAY FOR THROMBIN ACTIVITY AND INHIBITION BY RNA LIGANDS.

The hydrolysis by thrombin of the chromogenic substrate S-2238 (H-D-Phe-Pip-Arg-pNltroaniline [H-D-Phe-Pip-Arg-pNA]) (Kabi Pharmacia) was measured photometrically at 405 nm due to the release of p-nitroaniline (pNA) from the substrate.

Thrombin
H-D-Phe-Pip-Arg-pNA + H₂O ----->

H-D-Phe-Pip-Arg-OH + pNA

Thrombin was added to a final concentration of 10^{-4} or 10^{-5} M to a reaction buffer (50 mM sodium citrate, pH 6.5, 150 mM NaCl, 0.1% PBG), containing 250 μ M S2238 substrate at 37 °C. For inhibition assays, thrombin plus RNA (equimolar or at 10-fold excess) were preincubated 30 secs at 37 °C before adding to the reaction mixture

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(Table XIV).

EXAMPLE 17. FIBRINOGEN CLOTTING.

Thrombin was added for a final concentration of 2.5 nM to 400 μ l incubation buffer (20 mM Tris-acetate, pH 7.4, 140 mM NaCl, 5 mM KCl, 1 mM CaCl₂, 1 mM MgCl₂) containing 0.25 mg/ml fibrinogen and 1 U/1 RNAse inhibitor (RNasin, Promega) with or without 30 nM RNA Class I or 60 nM RNA Class II at 37 °C. Time in seconds from addition of thrombin to clot formation was measured by the tilt test (Table XIV).

EXAMPLE 18. SPECIFICITY OF THROMBIN BINDING.

The binding affinity of the full-length class I RNA 16 (SEQ ID NO:198), class II RNA 27 (SEQ ID NO:209) and bulk 30N3 RNA for the serum proteins Antithrombin III (ATIII) and Prothrombin was determined by filter binding, as described above for the evolution of high affinity RNA ligands (Example 10). These experiments were done in protein excess at concentrations from 1×10^{-5} to 5×10^{-6} M at a final RNA concentration of 2×10^{-4} M (Figure 11).

EXAMPLE 19. EVOLUTION OF HIGH AFFINITY DNA LIGANDS TO THROMBIN.

High affinity single-stranded DNA (ssDNA) ligands for thrombin were isolated by SELEX. Two populations of approximately 10^{14} ssDNA molecules with either a 30-nucleotide (30N) (SEQ ID NO:215) or 60-nucleotide (60N) (SEQ ID NO:260) variable region and 5' and 3' fixed regions were synthesized for the initial selection. Thrombin and DNA were incubated in a buffer containing 50 mM Tris-Cl, pH 7.5, 100 mM NaCl, 1 mM MgCl₂ at 37 °C for 5 minutes. The thrombin-bound DNA was partitioned from unbound DNA by nitrocellulose-filter binding. DNA was eluted from the filters by denaturation and

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phenol/chloroform extraction. A double-stranded DNA product with 3 biotin molecules at the 5' end of the complementary strand was created and amplified by PCR using a 3' complementary biotinylated primer and sense 5' primer. The double-stranded product was bound to a streptavidin-agarose matrix and the nonbiotinylated ssDNA template was isolated by alkaline denaturation. This ssDNA template pool was used for the following round of SELEX.

10 Nitrocellulose filter binding was used to determine K_{ds} . No additional improvement in binding was seen after 12 rounds of SELEX where the K_{ds} for the 30N and 60N populations were both determined to be approximately 8 nM (Figure 12). The K_{ds} for the bulk 30N and 60N populations after 12 rounds of SELEX were approximately 8 μ M and 5 μ M, respectively. Double-stranded DNA from the 12th round was digested with restriction enzyme sites in the 5' and 3' fixed regions and ligated into the complementary sites of the *E. coli* cloning vector pUC18. Plasmid DNA was prepared and used for dideoxy sequencing by PCR. Twenty-eight clones from the 30N population were sequenced and 24 unique sequences were identified while thirty-two clones from 60N population were sequenced and 31 unique sequences were identified (Table XV). ssDNA from individual clones 6 (SEQ ID NO:219), 8 (SEQ ID NO:221), 14 (SEQ ID NO:224), 16 (SEQ ID NO:226), and 35 (SEQ ID NO:238) from the 30N population and 7 (SEQ ID NO:236), 18 (SEQ ID NO:256), and 27 (SEQ ID NO:264) from the 60N population was prepared and K_{ds} were determined by nitrocellulose filter binding. K_{ds} ranged from 0.4 nM to 9.4 nM for the 30N DNAs and from 0.9 to 2.5 nM for the 60N DNAs (Table XVI). Regions of homology between these DNAs are indicated in bold and G-nucleotide residues that may be involved in quadruplex formation are also underlined. A truncated ligand of 38 nucleotides from

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the high affinity clone 60-18 (SEQ ID NO:278) ($K_{d}=0.9$ nM), designated 60-18(38) (SEQ ID NO:279) has been identified ($K_{d}=1.9$ nM; Table XVI) that retains high-affinity binding (Figure 13) and inhibits clotting (Figure 14).

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NEXAGENFIGURETABLE.1-TEAM

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NEXACENFIGURESTABLE 2-2AM

TABLE III. FAMILY 2 SEQUENCES FROM SELEX EXPERIMENTS A AND B.

CONSENSUS SEQUENCE:
RRGGHAAACGYWNNGDCAAGNNCACYY
(SEQ ID NO:23)

gggagcucagaaauaacgcucaa-[30N]-uucgacaugaggcccggaucggc (SEQ ID NO:1)

| FAMILY 2 | CLONE (30N) | SEQ ID NO. |
|----------|---------------------------------|--------------|
| 11A | GGGUAACGUUGU GACAAGUACACCGCGUC | SEQ ID NO:24 |
| 12A | GGGGCAACGCUACA GACAAGUGCACCCAAC | SEQ ID NO:25 |
| 26A | CGUCAGAAGGCAACGUUA GCAAGCACAC | SEQ ID NO:26 |
| 27A | CCUCUCGAAGACAACGUGU GACAAG ACAC | SEQ ID NO:27 |
| 47A | AGUGGGAACGCUACUUGACAAG ACACCAC | SEQ ID NO:28 |
| 65A | GGCUACGCUAAU GACAAGUGCACUUGGGUG | SEQ ID NO:29 |

gggagaugccugucgagcaugcug-[30N]-guagcuaaacagcuuugucgacggg (SEQ ID NO:4)

| FAMILY 2 | CLONE (30N) | SEQ ID NO. |
|----------|---------------------------------|--------------|
| 1B | CUCUGGUAACGCAAU GUCAAGUGCACAUGA | SEQ ID NO:30 |
| 2B | AGCCGCAGGUAACGGACC GGCGAGACCAU | SEQ ID NO:31 |
| 6B | ACGAGCUUCGUAACGCUAUC GACAAGUGCA | SEQ ID NO:32 |
| 8B | AAGGGGAAACGUUGA GUCCGGUACACCCUG | SEQ ID NO:33 |
| 9B | AGGGUACGUACU GGCAAGCUCACCUACG | SEQ ID NO:34 |

TABLE III. (CONTINUED)

| | | |
|-----|----------------------------------|--------------|
| 11B | GAGGUAACGUAC GACAAGACCACUCCAACU | SEQ ID NO:35 |
| 12B | AGGUAACGCUGA GUCAAGUGCACUCGACAU | SEQ ID NO:36 |
| 13B | GGGAAACGCUAUC GACGAGUGCACCCGGCA | SEQ ID NO:37 |
| 14B | CCGAGGGUAACGUUGG GUCAAGCACACCU | SEQ ID NO:38 |
| 15B | UCGGGGUAACGUUUU GGCAAGGC ACCCGAC | SEQ ID NO:39 |
| 19B | GGUAACGUGUG GACAAGUGCACACGUGC | SEQ ID NO:40 |
| 22B | AGGGUACGUACU GGCAAGCUCACCUACG | SEQ ID NO:41 |
| 28B | AGGGUACGUUAU GUCAAGAC ACCUCAAGU | SEQ ID NO:42 |
| 29B | GGGUAACGCAUU GGCAAGAC ACCCAGCCCC | SEQ ID NO:43 |
| 36B | GAGGAAACGUACC GUCGAGCC ACUCCAUGC | SEQ ID NO:44 |
| 38B | AGGUAACGUGA GUCAAGUGCACUCGACAU | SEQ ID NO:45 |
| 48B | GGGUAACGUGU GACAAGAUACCCAGUUUG | SEQ ID NO:46 |
| 49B | CACAGGGCAACGUGCU GACAAGUGCACCU | SEQ ID NO:47 |

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TABLE IV. OTHER SEQUENCES FROM SELEX
EXPERIMENTS A AND B.

gggagcucagaaacgcucua-[30N]-uucgacaugaggcccgauccggc (SEQ ID NO:1)

| NUMBER | CLONE (30N) | SEQ ID NO. |
|--------|--------------------------------|---------------|
| 8A | ACGCCAAGUGAGUCAGCAACAGAGCGUCCG | SEQ ID NO: 48 |
| 9A | CCAGUGAGUCCUGGUAUCCGCAUCGGGCU | SEQ ID NO: 49 |
| 24A | CUUCAGAACGGCAUAGUGGUCGGCCGCGCC | SEQ ID NO: 50 |
| 33A | AGGUCACUGCGUCACCGUACAUGCCUGGCC | SEQ ID NO: 51 |
| 34A | UCCAACGAACGGCCUUCGUAUUCAGCCACC | SEQ ID NO: 52 |
| 36A | ACUGGAACCUGACGUAGUACAGCGACCCUC | SEQ ID NO: 53 |
| 37A | UCUCGCGCGCCUACACGGCAUGCCGGGA | SEQ ID NO: 54 |
| 40A | GAUCACUGCGCAAUGCCUGCAUACCUGGUC | SEQ ID NO: 55 |
| 43A | UCUCGCGCGCCUACACGGCAUGCCGGGA | SEQ ID NO: 56 |
| 44A | UGACCAGCUGCAUCCGACGAUAUACCCUGG | SEQ ID NO: 57 |
| 45A | GGCACACUCCAACGAGGUAACGUACGGCG | SEQ ID NO: 58 |
| 55A | AGCGGAACGCCACGUAGUACGCCGACCCUC | SEQ ID NO: 59 |

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TABLE IV. (CONTINUED)

gggagauccugucgagcaugcug-[30N]-guagcuaaacagcuuugucgacggg (SEQ ID NO:4)

| NUMBER | CLONE (30N) | SEQ ID NO. |
|--------|--------------------------------|---------------|
| 4B | ACCCACGCCCCACAACCGAUGAGUUCUCGG | SEQ ID NO: 60 |
| 5B | UGCUUGAAGUCCUCCCGCCUCUCGAGGU | SEQ ID NO: 61 |
| 7B | AUGCUGAGGAUAUUGUGACCACUUCGGCGU | SEQ ID NO: 62 |
| 16B | ACCCACGCCCCACAACCGAUGAGCUCGGA | SEQ ID NO: 63 |
| 20B | AGUCCGGAUGCCCCACUGGGACUACAUGU | SEQ ID NO: 64 |
| 21B | AAGUCCGAUUGCCACUGGGACUACCACUGA | SEQ ID NO: 65 |
| 23B | ACUCUCACUGCGAUUCGAAAUCAUGCCUGG | SEQ ID NO: 66 |
| 40B | AGGCUGGGUACCGACAACUGCCCGCCAGC | SEQ ID NO: 67 |
| 42B | AGCCGAGGUAACGGACCGGCGAGACCACU | SEQ ID NO: 68 |
| 26B | GCAUGAAGCGGAACUGUAGUACGCGAUCCA | SEQ ID NO: 69 |

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TABLE V. REPEAT SEQUENCES FROM SELEX
EXPERIMENTS A AND B.

gggagcucagaaaacgcucaa-[30N]-uucgacaugaggccggauccggc (SEQ ID NO:1)

| NUMBER | SEQ ID NO. | CLONE REPEATED |
|------------------------------------|--------------|-------------------|
| 3A GGGUAAACGUUGUGACAAGUACACCGCGUC | SEQ ID NO:70 | 11A |
| 15A GGGUAAACGUUGUGACAAGUACACCGCGUC | SEQ ID NO:71 | 11A |
| 20A GGGUAAACGUUGUGACAAGUACACCGCGUC | SEQ ID NO:72 | 11A |
| 48A GGGUAAACGUUGUGACAACUACACCGCGUC | SEQ ID NO:73 | 11A |
| 58A GGGUAAACGUUGUGACAACUACACCGCGUC | SEQ ID NO:74 | 11A |
| 64A GGGUAAACGUUGUGACAACUACACCGCGUC | SEQ ID NO:75 | 11A |
| 28A CGUCAGAAGGCAACGUUAAGGCAAGCACAC | SEQ ID NO:76 | 26A |
| 30A GUAGCACUAUCGGCCUAACCCGUAAGCUCC | SEQ ID NO:77 | 10A |
| 23A ACCCGCGGCCUCCGAAGCUAACCAAGACAC | SEQ ID NO:78 | 13A |
| 46A AGGUCACUGCGUACCGUACAUGCCUGGCC | SEQ ID NO:79 | 33A |
| 49A AGGUCACUGCGUACCGUACAUGCCUGGCC | SEQ ID NO:80 | 33A |
| 50A GGCAACUCCAACGAGGUAACGUUACGGCG | SEQ ID NO:81 | 45A |
| 41A GGGGCAACGCUACAGACAAGUGCACCCAAC | SEQ ID NO:82 | 12A |
| 51A GGGGCAACGCUACAGACAAGUGCACCCAAC | SEQ ID NO:83 | 12A |
| 54A GGGGCAACGCUACAGACAAGUGCACCCAAC | SEQ ID NO:84 | 12A |
| 35A UGGGUGCUAACCAGGACACCCACGCGU | SEQ ID NO:85 | 14A |

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TABLE V. (CONTINUED)

gggagugccugucgagcaugcug-[30N]-gungcuaaacagcuuugucgacggg (SEQ ID NO:4)

| NUMBER | SEQ ID NO. | CLONE REPEATED |
|-------------------------------------|--------------|-------------------|
| 18B CCGAGGGUAAACGUUGGGUCAAGCACACCUC | SEQ ID NO:86 | 14B |
| 24B GGGAAACGCUAUCGACGAGUGCACCCGGCA | SEQ ID NO:87 | 13B |
| 39B GGGAAACGCUAUCGACGAGUGCACCCGGCA | SEQ ID NO:88 | 13B |
| 37B ACUCUCACUGCGAUUCGAAAUCAUGCCUGG | SEQ ID NO:89 | 23B |
| 43B GCAUGAAGCGGAACUGUAGUACGCGAUCCA | SEQ ID NO:90 | 26B |
| 46B GCAUGAAGCGGAACUGUAGUACGCGAUCCA | SEQ ID NO:91 | 26B |
| 25B AGGGUAAACGUACUGGCAAGCUCACCUACGC | SEQ ID NO:92 | 9B |
| 33B AGGGUAAACGUACUGGCAAGCUCACCUACGC | SEQ ID NO:93 | 9B |
| 31B GUUAACGCUUGGACAAGUGCACCAGCUGC | SEQ ID NO:94 | 19B |

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TABLE VI. SECONDARY STRUCTURES AND DISSOCIATION CONSTANTS (K_d 's) FOR A REPRESENTATIVE SET OF HIGH-AFFINITY LIGANDS FROM FAMILY 1.

| LIGAND | STRUCTURE ^a | K_d , nM | SEQ ID NO: (PARENT SEQUENCE) |
|--------------------|--|------------|------------------------------------|
| 5A-t ^b | CC AA CCUC GUCGAA---GCU C ggag cagcuu CGG C ua CAC U | 23 ± 3 | 190 |
| 7A-t ^b | AA CGGCGAG---CU C GUCGCUC GA C ACA A | 5.0 ± 0.5 | 191 |
| 13A-t ^b | C A CCG GGCCUC---CGAAG---CU A ggc-cgggag gcuu C GA C uaca ACAG C | 3.2 ± 0.5 | 193 |

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TABLE VI. (CONTINUED)

| LIGAND | STRUCTURE ^a | K_d , nM | SEQ ID NO: (PARENT SEQUENCE) |
|--------------------|--|------------|------------------------------------|
| 14A-t ^b | cucaa A aaacg UGGGUG---CU A uuUGU- -ACCCAC GA C CGC ACAG C | 3.0 ± 0.5 | 194 |
| 21A-t ^b | A aaU---GGGU---GCUU A uUG CCCA CGGA C UCGU CAC C | 8.1 ± 0.8 | 197 |
| 25A-t ^b | A CUA-GGUG---CU U GGU CCUC GA C C UCAG C | 5.9 ± 1.4 | 198 |
| 39A-t ^b | CU A AACCAG GC--GUGC A uuGGUC--CG CACG C UA C | 8.5 ± 1.2 | 201 |

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^aStrongly conserved positions are shown in boldface symbols. Nucleotides in the constant region are in lowercase type.

^bThe letter "t" is used to designate truncated sequences derived from the corresponding parent sequences (Figure XVII).

REVISION/P101032/PM101.6-5-95

TABLE VII. SECONDARY STRUCTURES AND DISSOCIATION CONSTANTS (K_d 's)
FOR A REPRESENTATIVE SET OF HIGH-AFFINITY LIGANDS FROM FAMILY 2.

| LIGAND | STRUCTURE ^a | K_d , nM | SEQ ID NO: (PARENT SEQUENCE) |
|--------------------|---|---------------|---------------------------------|
| 12A-t ^b | <pre> CAACGCU G A C uc-aa---GGG A ag uu CCC G c CAA A A CGUGAAC </pre> | 0.9 ± 0.2 | 204 |
| 26A-t ^b | <pre> CAACGUA A U G A GUC GAAG G cag-cuuC G A G CACGAAC </pre> | 0.4 ± 0.1 | 205 |

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TABLE VII. (CONTINUED)

| LIGAND | STRUCTURE ^a | K_d , nM | SEQ ID NO: (PARENT SEQUENCE) |
|--------------------|--|----------------|---------------------------------|
| 65A-t ^b | <pre> CUACGUA G A A aacgcucuaag U uuGUGGGUUC G A A CGUGAAC </pre> | 0.6 ± 0.04 | 208 |
| 22B-t ^b | <pre> UAACGUA G C agc-augcugAGG U ucg ugCGACUCC G a A CUCGAAC </pre> | 1 ± 0.6 | 220 |
| 28B-t ^b | <pre> UAACGUA G U augc-ugAGG A ugUG ACUCC G A A CAGAACU </pre> | 2 ± 1 | 221 |

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TABLE VII. (CONTINUED)

| LIGAND | STRUCTURE* | K _d , nM | SEQ ID NO: (PARENT SEQUENCE) |
|--------------------|--|---------------------|---------------------------------|
| 38B-t ^b | <pre> UAACGCU C G G gcaug ugAG A ugUAC GCUC G A A U CGUGAAC </pre> | 4 ± 1 | 224 |
| 2B-t ^b | <pre> UAACGCA C G C AGC GCAG C ucg ugUU G a A G CCAGAGC </pre> | 170 ± 80 | 210 |

*Strongly conserved positions are shown in boldface symbols. Nucleotides in the constant region are in lowercase type.

^bThe letter "t" is used to designate truncated sequences derived from the corresponding patent sequences (Figure XVIII).

RELATION/FIGURES/TABLE 7-8M

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TABLE VIII. 2'-NH₂ RNA LIGANDS TO bFGF*.

5'-GGGAGACAAGAAUAACGCUCAA [-30N-] UUCGACAGGAGGCUCACAACAGGC-3' (SEQ ID NO:95)
 5'-GGGAGGACGAUGCGG [-50N-] CAGACGACTCGCCCGA-3' (SEQ ID NO:98)

FAMILY 1A

| | | CORRESPONDING CLONE | SEQ ID NO: |
|-----|--|------------------------|------------------|
| 14A | ACANGGAGUUGUGUGGAAGGCAGGGGGAGG | 30N | 101 |
| 15A | UGUGUGGAAGGCAGUGGGAGGUUCAGUGGU | 30N | 102 |
| 17A | AAAGUUGUGUGGAAGACAGUGGGAGGUGAA | 30N | 103 |
| 21A | GUAGACUAAUGUGUGGAAGACAGCGGGUGG | 30N | 104 |
| 29A | NNAGUUGUGUGGAAGACAGUGGGGGUUGA | 30N | 105 |
| 38A | GGUGUGUNGAAGACAGUGGGGUNGUUAGNC | 30N | 106 |
| 49A | AUGGUGUGUGGAAGACAGUGGGUGGUUGCA | 30N | 107 |
| 54A | ACUGUUGUGUGGAAGACAGCGGGUGGUUGA | 30N | 108 |
| 60A | AAUGUAGGCUGUGUGGUAGACAGUGGGUGG | 30N | 109 |
| 68A | GAUGUGUGGAGGGCAGUGGGGGUACCAUA | 30N | 110 |
| 74A | GGGGUCAAGGACAGUGGGUGGUGGUGU | 30N | 111 |
| 16B | UGCUGCGGUGCGCAUGUGUGGAAGACAGAGGGAGGUUAGAAUCAUGACGU | 50N | 112 |
| 31B | ACAGACCGUGUGUGGAAGACAGUGGGAGGUUAAUUAACGUAGUGAUGGCCGC | 50N | 113 |
| 38B | GCUGCGGUGCGCAUGUGUGGAAGACAGAGGGAGGUUAGAAUCGUGCCGC | 50N | 114 |
| 39B | GAAAACUACGGUGUGUGGAAGACAGUGGGAGGUUGGCAGUCUGUGUCCGU | 50N | 115 |

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W0 952183

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TABLE VIII. (CONTINUED)

FAMILY 1A

| | | CORRESPONDING CLONE | SEQ ID NO: |
|-----|---|------------------------|------------------|
| 62B | UCCAUCGUGGAAGACAGUGGGAGGUUAGAAUCAUGACGUCAGACGACUC | 50N | 116 |
| 79B | UGUGAUUUGUGUGGAAGGCAGUGGGAGGUGUCGAUGUAGAUUCUGGCGAUG | 50N | 117 |
| | UGUGUGGAAGACAGUGGGWGGUU | ★ | 118 |

FAMILY 1B

| | | | |
|-----|---|-----|-----|
| 59A | UGUGUGGAAGGGUACCUGAGU----GGGGAUGGG | 30N | 119 |
| 82A | AAGACUGUGUGGAAGGGG---UGUA----GGGGUUGGG | 30N | 120 |
| 3B | UAGGGCCGCAACUGUGUGGAAGGGAGGAUGCGUCAUGGGGGUUGGGCUG | 50N | 121 |
| | UGUGUGGAAGGGNNNNUGNGU----GGGGUUGGG | ★ | 122 |

FAMILY 1C

| | | | |
|-----|---|-----|-----|
| 1B | AUUGUGUGGGAUAG-GGCAUAGA-GGGUGU-GGGAAACCCAGACCGGGGCGU | 50N | 123 |
| 43B | UGUGUGGGACAGCGG-AUC-AGGGGUGU-GGGAGCGCAUAACAUCUACNUGCU | 50N | 124 |
| 30B | ANNNNUNUGCAUGUGUGGGACAG-GGUGCAUGUGGGUUGCGGGACCUUGGU | 50N | 125 |
| | UGUGUGGGACAG-GGNAUAMANGGUGU-GGGA | ★ | 126 |

FAMILY 2

| | | | |
|-----|--------------------------------|-----|-----|
| 51A | GCAGGAGGAUAGGGAUCGGAUGGGGUAGGA | 30N | 127 |
|-----|--------------------------------|-----|-----|

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TABLE VIII. (CONTINUED)

FAMILY 2

| | | CORRESPONDING CLONE | SEQ ID NO: |
|-----|--|------------------------|------------------|
| 53A | UGAGGAUCGGAUGGGGAGCAGGCCGAGGAA | 30N | 128 |
| 67A | GUGGAUUGGAAGGGGUGCUGGAGGAGGACG | 30N | 129 |
| 15B | UAGGAAUGGAUGGGGUUGGAACAGAGUUCUAAUGUCGACCUCACAUGUGG | 50N | 130 |
| 77B | CAGGAAUGGAUGGGGUUGGAACAGAGUUCUAAUGUCGACCUCACAUGCGU | 50N | 131 |
| 48B | CAGGAUAGGAUGGGGUCGGAACCGUGUAUCAUAACGAGUCAUCUCCUGGU | 50N | 132 |
| | GGAUHGGAUGGGGU | ★ | 133 |

FAMILY 3

| | | | |
|-----|---|-----|-----|
| 58A | UUAACGGCGUGGUCCGAGGGUGGCGAGUAC | 30N | 134 |
| 64A | GACUAGGCGCGGACCGUGGGUGGUGAGUGG | 30N | 135 |
| 50B | AGUGGCAUGGGCCGUGGGAGGUGAGUGUCGAGACUGGUGUUGGGCCU | 50N | 136 |
| 22B | CGUGGUUCCGUGGGUGGUGAGAUGAGACUUAUACAGUUCGUAGACCGGU | 50N | 137 |
| | CCGUGGGUGGUGAGU | ★ | 138 |

TWO-MEMBER FAMILIES

| | | | |
|-----|--|-----|-----|
| 35B | NAAAUACGAGAGAGGANCAUANNUGACUGAACAUUGAUGUAUUAACGAGU | 50N | 139 |
| 49B | GAGGUACGAGAGAGGAGCGUAGGUGACUGAACAUUGAUGUAUUAACGUGU | 50N | 140 |
| 47B | AGGGUGGCUGGGAGGACCCGCGUGAAUCGGUAGCACAGUGAUGUUCGGU | 50N | 141 |
| 73B | GAGGGUGGCAGGGAGGACCCGCGUGAAUCGGUAGCACAGUGAGUUCGGU | 50N | 142 |
| 6A | CGCGAGGGCUGGCGGGUAGGAUGGGUAGA | 30N | 143 |
| 75B | CGCGAGUGCUACGAGGCGUGGGGGGUGGAAACUAGUUGUGCUUCGGCCG | 50N | 144 |

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TABLE VIII. (CONTINUED)

TWO-MEMBER FAMILIES

55A GAUUGGAAGCAGGGUGUGGGUAGGAGGGC
 21B GACCACAGUUAAACGCCCAUCAGUGGUAGGGUGUGGGUAAAGGAGGGCUG

CORRES-
PONDING
CLONESEQ
ID
NO:

30N 145
 50N 146

OTHER SEQUENCES

6A CGCGAGGGCUGGCGGGUAGGAUGGGUAGA
 9A UGGGCCGCCGGUCUUGGGUGUAUGUGUGAA
 52A AGUUGGGGGCUCGUGCGGCGUGGGCGGUGC
 62A GGGAUGGUUGGAGACCGGGAGAUUGGGAGGA
 69A AAACGGGGCGAUGGAAAGUGUGGGGUACGA
 73A GAGGAGGAUGGAGAGGAGCGGUGUGCAGGG
 83A GAGAGGGUGAAGUGGGCAGGAUGGGGUAGG
 8B CUGAAAUUGCGGGUGUGGAGGUAGCUGGGAAAGGUGGAUGGUACACGU
 13B CAAUGUUUGGAGUCUGCUAUGUGGGUGGGUAGACGUACCGAUGGUUGC
 14B ACGGGGAAGUACGAGAGCGGACUGUAAGUCUAGUGGGUCAGUUCGGUG
 19B UUCAGCGCGCAUUAUGUCAGCGGUUCAACAAAAGAGGUGUUCGUGUGUG
 26B CGGAUUGUGUGGUCGGGAGGGCAGUAGUUUACACUCACCGUGGUCUGCU
 29B GGUUGUGACAAUGUGCGUGGGUUGGGCAGGUACAAAGCGUAUGGGCGUG
 34B AACGGGAGGUACGAGAGCGGGAGCGCAUAAUAGGAAACUCCUUGCACGU
 36B AGGCAGUAUUGGGGUGGUCAGCGCCUCCCCAAAACUCGCACCUUAGCCC

30N 147
 30N 148
 30N 149
 30N 150
 30N 151
 30N 152
 30N 153
 50N 154
 50N 155
 50N 156
 50N 157
 50N 158
 50N 159
 50N 160
 50N 161

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TABLE VIII. (CONTINUED)

OTHER SEQUENCES

44B GGGUUGGGUGGCAAGCGGAGAGCAGGGUAGGUGCGGACUCAUUGGUGUG
 52B GGAGGGGCAGGUUCGAUGCGGGAGCGACUGACCACGAGAAAUGUGCGGGU
 72B CUCAGCAUCCAGGAAGGGGACUUGGUAGGGCACCAUCGAGAUUCUUGGCGU
 78B ACCCUAGGCAUCCAGGUUGGGGAUAGCGGUUGGAGUGAAUGUGUUGUGCC

CORRES-
PONDING
CLONESEQ
ID
NO:

50N 162
 50N 163
 50N 164
 50N 165

NITROCELLULOSE-BINDING FAMILY

5A CACGGAGGAGGAGGUCAGACUUAGCGGUCA
 16A UACAGGGGAAGGAGNGAAUUGCAAGAUGAA
 17A* AAAGUUGUGUGGAAGACAGUGGGAGGUGAA
 19A UGAUGGCGGUAGUGGAGGUAAUGAGCGUNA
 25A UAGGAGGUUGGAGGAAAGCUUCACAGCCGA
 40A UGAGGAGGAGGAGGACAGGAUUCACAGAU
 65A GUUAGGAGGGUGGAGGUUCGAGUGUGGCAA
 66A CGUCGAGUGCGAUGGAGGAGGAGGGAUGCA
 74A* GGGGUCAAGGACAGUGGGUGGUGGUGUGU
 75A GGAGGGAGGAGGGAUGAUGAGCUCAUCAGC
 76A CAAACAGGAGGGAAUGGAGGGNG
 77A AGGGGUGGUCGGUAAGCUCGGUGGUGGUGG
 78A AGGAGGGUUAAGGAGGGAGAUUAAGCGUUGG

30N 166
 30N 167
 30N 168
 30N 169
 30N 170
 30N 171
 30N 172
 30N 173
 30N 174
 30N 175
 30N 176
 30N 177
 30N 178

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TABLE VIII. (CONTINUED)
NITROCELLULOSE-BINDING FAMILY

| | CORRESPONDING CLONE | SEQ ID NO: |
|--|------------------------|------------------|
| 81A GUGGAGGGUACGUGGAGGGGAGAGCGACA | 30N | 179 |
| 85A AUAUUCAAGGAGGUGGAGGACAGAUGCGC | 30N | 180 |
| 86A GAUGAGGACUCGGGGCGAGGGUGGUACCA | 30N | 181 |
| 5B AGGUCGUGGCUGGGAUUCGUCCUCGACAUUGUGGCUCUGGUGCC | 50N | 182 |
| 6B AAGUUAGUCAUCGUGCAAACUGCGAGUGCACUGCUCGGGAUCC | 50N | 183 |
| 21B GACCACAGUUUAAACGCCCAUCAGUGGUAGGGUGUGGGUAAGGAGGGCUG | 50N | 184 |
| 75B CGCGAGUGCUACGAGGCGUGGGGGGUGGAAACUAGUUGUGCUCUGGCCG | 50N | 185 |

* CONSENSUS SEQUENCE

* NUCLEOTIDE ABBREVIATIONS C AND U ACTUALLY DEPICT THE MODIFIED NUCLEOTIDES 2'-NH₂-C AND 2'-NH₂-U.

RECEIVED/FIGURES/TABLES: 9-84N

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TABLE IX. DISSOCIATION CONSTANTS FOR A
REPRESENTATIVE SET OF HIGH-AFFINITY
2'-NH₂ RNA LIGANDS TO bFGF.

| CLONE | Kd (nM) | SEQ ID. NO: |
|-----------------------|-----------|-------------|
| 21A | 1.3 ± 0.1 | 104 |
| 49A | 1.4 ± 0.3 | 107 |
| 53A | 1.5 ± 0.3 | 128 |
| 54A | 1.7 ± 0.3 | 108 |
| 58A | 1.4 ± 0.3 | 134 |
| 59A | 1.2 ± 0.2 | 119 |
| 22B | 2.8 ± 0.5 | 137 |
| 34B | 2.0 ± 0.4 | 160 |
| 47B | 2.9 ± 0.3 | 141 |
| 48B | 6.7 ± 1.1 | 132 |
| 52B | 2.3 ± 0.3 | 163 |
| 72B | 3.4 ± 0.5 | 164 |
| starting random RNA A | 65 ± 11 | |
| starting random RNA B | 240 ± 140 | |

RECEIVED/FIGURES/TABLES: 9-84N

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TABLE X. INHIBITION OF RAT CORNEAL VASCULAR
INGROWTH BY RNA LIGAND 21A.

| Day | Group I (untreated) | Group II 21A | Group III (bFGF) | Group IV (21A + bFGF) |
|-----|------------------------|-----------------|---------------------|--------------------------|
| 7 | 367 ± 4 | 363 ± 3 | 972 ± 72 | 623 ± 122* |
| 14 | 470 ± 57 | 388 ± 11 | 1528 ± 167 | 900 ± 80* |

Data are mean ± STD. Err.

*p < 0.05 compared with Group III. (T-test, 2 Tailed)

RESEARCH/FIGURES/TABLE. 10-2AM

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TABLE XI. OLIGONUCLEOTIDES USED IN SELEX EXPERIMENTS A AND B
TO SELECT 2'-NH₂ PYRIMIDINE RNA LIGANDS TO bFGF.

SELEX EXPERIMENT A

SEQ ID NO.

Starting RNA* 5'-GGGAGACAAGAAUAACGCUCAA [-30N]-JUUCGACAGGAGGCUCACAACAGGC-3'

SEQ ID NO:95

PCR Primer 1 5'-TAATACGACTCACTATAGGGAGACAAGAAUAACGCUCAA-3'
T7 Promoter

SEQ ID NO:96

PCR Primer 2 5'-GCCTGTTGTGAGCCTCCTGTCGAA-3'

SEQ ID NO:97

SELEX EXPERIMENT B

SEQ ID NO.

Starting RNA* 5'-GGGAGGACGAUGCGG [-50N]-CAGACGACTCGCCCGA-3'

SEQ ID NO:98

PCR Primer 1 5'-TAATACGACTCACTATAGGGAGGACGAUGCGG-3'
T7 Promoter

SEQ ID NO:99

PCR Primer 2 5'-TCGGGCGAGTCGTCTG-3'

SEQ ID NO:100

* In the randomized region; [-30N-] or [-50N-]; each pyrimidine contains an amino (-NH₂) functionality at the 2'-position.

RESEARCH/FIGURES/TABLE. 11-2AM

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TABLE XII. THROMBIN RNA BINDING SEQUENCES

| CLASS I | 1 | 2 | 3 | SEQ ID NO: |
|---------|-----------------------|----------------------------------|---------------------------|------------|
| #1 | AGAUGCCUGUCGAGCAUGCUG | AGGAUCGAAAGUUAAGUAGGCUUUGUGUCUC | GUAGCUAAACAGCUUUGUCGACGGG | 192 |
| #6 | AGAUGCCUGUCGAGCAUGCUG | AGGAUCGAAAGUUAAGUAGGCUUUGUGUCUC | GUAGCUAAACAGCUUUGUCGACGGG | 192 |
| #13 | AGAUGCCUGUCGAGCAUGCUG | AGGAUCGAAAGUUAAGUAGGCUUUGUGUCUC | GUAGCUAAACAGCUUUGUCGACGGG | 192 |
| #19 | AGAUGCCUGUCGAGCAUGCUG | AGGAUCGAAAGUUAAGUAGGCUUUGUGUCUC | GUAGCUAAACAGCUUUGUCGACGGG | 192 |
| #23 | AGAUGCCUGUCGAGCAUGCUG | AGGAUCGAAAGUUAAGUAGGCUUUGUGUCUC | GUAGCUAAACAGCUUUGUCGACGGG | 192 |
| #24 | AGAUGCCUGUCGAGCAUGCUG | AGGAUCGAAAGUUAAGUAGGCUUUGUGUCUC | GUAGCUAAACAGCUUUGUCGACGGG | 192 |
| #25 | AGAUGCCUGUCGAGCAUGCUG | AGGAUCGAAAGUUAAGUAGGCUUUGUGUCUC | GUAGCUAAACAGCUUUGUCGACGGG | 192 |
| #30 | AGAUGCCUGUCGAGCAUGCUG | AGGAUCGAAAGUUAAGUAGGCUUUGUGUCUC | GUAGCUAAACAGCUUUGUCGACGGG | 192 |
| #2 | AGAUGCCUGUCGAGCAUGCUG | UACUGGAGCGAAGGUAGUAGGCAGUCAC | GUAGCUAAACAGCUUUGUCGACGGG | 193 |
| #5 | AGAUGCCUGUCGAGCAUGCUG | AUAUCACCGAUCGAAAGGAAGUAGGCGUG | GUAGCUAAACAGCUUUGUCGACGGG | 194 |
| #9 | AGAUGCCUGUCGAGCAUGCUG | CCUUCGCCGGUUCGAAAGUCAGUAGGCGG | GUAGCUAAACAGCUUUGUCGACGGG | 195 |
| #10 | AGAUGCCUGUCGAGCAUGCUG | CACCCGGAUCGAAAGUUAAGUAGGCGUGAGU | GUAGCUAAACAGCUUUGUCGACGGG | 196 |
| #15 | AGAUGCCUGUCGAGCAUGCUG | UGUAGCGAUCGAAAGGUAGUAGGCAGGUAC | GUAGCUAAACAGCUUUGUCGACGGG | 197 |
| #16 | AGAUGCCUGUCGAGCAUGCUG | CAUCCGGAUCGAAAGUUAAGUAGGCGGAGGUG | GUAGCUAAACAGCUUUGUCGACGGG | 198 |
| #18 | AGAUGCCUGUCGAGCAUGCUG | AUUGUUGCGGAUCGAAAGUUAAGUAGGCGCUA | GUAGCUAAACAGCUUUGUCGACGGG | 199 |

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TABLE XII. (CONTINUED)

| CLASS I (CONT.) | 1 | 2 | 3 | SEQ ID NO: |
|-----------------|-----------------------|--------------------------------------|---------------------------|------------|
| #21 | AGAUGCCUGUCGAGCAUGCUG | UGUACUGGAUCGAAAGGUAGUAGGCAGUCAC | GUAGCUAAACAGCUUUGUCGACGGG | 200 |
| #22 | AGAUGCCUGUCGAGCAUGCUG | AUCGAAAGUUAAGUAGGAGCGUUGU | GUAGCUAAACAGCUUUGUCGACGGG | 201 |
| #26 | AGAUGCCUGUCGAGCAUGCUG | ACCCUGGAGUCGGAUCGAAAGGUUAAGUAGGCGACU | GUAGCUAAACAGCUUUGUCGACGGG | 202 |
| #31 | AGAUGCCUGUCGAGCAUGCUG | GCGUCCGAUCGAAAGGUUAAGUAGGCGGACU | GUAGCUAAACAGCUUUGUCGACGGG | 203 |
| #33 | AGAUGCCUGUCGAGCAUGCUG | AUAUCACCGAUCGAAAGGAAGUAGGCGG | GUAGCUAAACAGCUUUGUCGACGGG | 204 |
| #34 | AGAUGCCUGUCGAGCAUGCUG | UGUACUGGAUCGAAAGGUAGUAGGCAGGCAC | GUAGCUAAACAGCUUUGUCGACGGG | 205 |
| #37 | AGAUGCCUGUCGAGCAUGCUG | AUAUCACCGAUCGAAAGGAAGUAGGCGUG | GUAGCUAAACAGCUUUGUCGACGGG | 206 |
| CLASS II | | | | |
| #3 | AGAUGCCUGUCGAGCAUGCUG | <u>GUGCGGCUUUGGGCGCCGUGCUU</u> GGC | GUAGCUAAACAGCUUUGUCGACGGG | 207 |
| #20 | AGAUGCCUGUCGAGCAUGCUG | <u>GUGCGGCUUUGGGCGCCGUGCUU</u> AC | GUAGCUAAACAGCUUUGUCGACGGG | 208 |
| #27 | AGAUGCCUGUCGAGCAUGCUG | <u>GUGCGGCUUUGGGCGCCGUGCUU</u> UAC | GUAGCUAAACAGCUUUGUCGACGGG | 209 |
| #35 | AGAUGCCUGUCGAGCAUGCUG | <u>GUGCGGCUUUGGGCGCCGUGCUU</u> UAC | GUAGCUAAACAGCUUUGUCGACGGG | 210 |
| #38 | AGAUGCCUGUCGAGCAUGCUG | <u>GUGCGGCUUUGGGCGCCGUGCUU</u> UAC | GUAGCUAAACAGCUUUGUCGACGGG | 209 |
| #39 | AGAUGCCUGUCGAGCAUGCUG | <u>GUGCGGCUUUGGGCGCCGUGCUU</u> UAC | GUAGCUAAACAGCUUUGUCGACGGG | 209 |

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* THE CONSERVED SEQUENCE MOTIFS WITHIN THE 3' VARIABLE REGION ARE UNDERLINED.
 NEXAGEN/FOURSTAR/13-EAM

TABLE XIII. LIGANDS USED IN BOUNDARY EXPERIMENTS

| CLONE* | RANDOM REGION | SEQ ID NO: |
|-----------------|---|------------|
| CLASS I | | |
| 6 | gggagauccuguc [g [agcaugcug AGGAUCGAAAGUUAAGGCUUUGUGUCU] C guagcuaaacagcuuugucgacggg | 211 |
| 16 | gggagauccugucgagcau [gcug C [AU [CCGGAUCGAAAGUUAAGGCGGAG] GUG guagcuaaacagcuuugucgacggg | 212 |
| 18 | gggagauccugucgagcaugcug AUUGU [UGCGAUCGAAAGUGAGGCGCUA] guagcuaaacagcuuugucgacggg | 213 |
| CLASS II | | |
| 27 | gggagauccuguc [g [agcaugcug GUGCGGCUUUGGCGCCGUGCUU] GAC guagcuaaacagcuuugucgacggg | 214 |

* NUCLEOTIDES IN THE CONSTANT REGION ARE IN LOWER CASE TYPE.
 "I" DENOTES A 5' BOUNDARY AND "J" DENOTES A 3' BOUNDARY
 THE PROPOSED 2° STRUCTURES ARE SHOWN IN TABLE XIII.

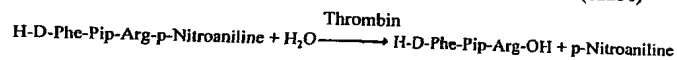
HEXAGEN/FIGURES/TABLE.13-EAM

PCT/US95/01458

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TABLE XIV. FUNCTIONAL ASSAYS THROMBIN ACTIVITY

A. Peptidase Activity-Cleavage of tripeptide p-nitroaniline substrate (S2238)



Measure the OD at 405nm for release of p-Nitroaniline

| | [Thrombin] | [RNA] | Inhibition (decrease in OD ₄₀₅) |
|------------------------------------|--------------------|--------------------|---|
| Class I RNA 16 (SEQ ID NO:198) | 10 ⁻⁴ M | 10 ⁻⁴ M | - |
| | 10 ⁻⁶ M | 10 ⁻⁷ M | - |
| | 10 ⁻⁸ M | 10 ⁻⁸ M | - |
| Class II RNA 27 (SEQ ID NO:209) | 10 ⁻⁴ M | 10 ⁻⁴ M | - |
| | 10 ⁻⁶ M | 10 ⁻⁷ M | - |
| | 10 ⁻⁸ M | 10 ⁻⁸ M | - |

B. Fibrinogen Clotting Assay

Ligand plus purified
human thrombin (2.5nM)

Clotting time (sec) for
purified fibrinogen (0.25 mg/ml)

| | |
|-----------------------------------|---------|
| No RNA/DNA | 65 |
| Class I RNA 16 (30nM) | 117 |
| Class II RNA 27 (60nM) | 115 |
| DNA 15mer G15D (SEQ ID NO:189) | 270-330 |

HEXAGEN/FIGURES/TABLE.14-EAM

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TABLE XV. HIGH-AFFINITY DNA LIGANDS TO THROMBIN

11TH ROUND 30N SEQUENCES

SEQ ID NO:

5'AGATGCTGTGAGCATGCT (30N) GTAGCTAACTGCTTTGTGACGGG

215

CLONE (30N)

| | | |
|-----------|--------------------------------|-----|
| #1 | TCACTAGGCTAGGTGTGATGATGCTAGTG | 216 |
| #2 | GTCACTACCTGTGTAGGGAAGGTGGAAT | 217 |
| #3 | ACTAGCGGGTAGTGGTGGTTGGGCTCTA | 218 |
| #6 | ACACCCGTGTAGGTAAGGATGGGTGGTC | 219 |
| #7, 23 | GCAATTGTGCTCTGTGTAGGTAAGGATGGG | 220 |
| #8, 9, 32 | GTGAATAGGTAGGTCGGATGGGCTACGGT | 221 |
| #10 | GAGTTGAGGGTAGGCTGGGATGGTGGAAC | 222 |
| #13 | ATGTGCTACCTGTGTAGGGAAGGATGGTGT | 223 |
| #14 | GTTGTGGTAGGGTTAGGATGGTAGCGGTT | 224 |
| #15, 34 | GTTGGCGGAGTGGTAGGCAGTAGGGTTGG | 225 |
| #16 | GCCGCTACGAGGGTAGGTGTGATGCTGCC | 226 |
| #17 | GTTTTGGTATAGGCTAGGTGTGATGATGCT | 227 |
| #18 | GTTTATCGGTAGGTTGGTTGGGCTACAAAT | 228 |
| #20 | ACGGACCGCGGACGAACTGTGAAGGGCCG | 229 |
| #21 | GCCTTAAGCTCGGGTAGTGGTGGGTTGGT | 230 |
| #25 | GAATCAGTTTAGGTGTGGTAGGCAGGTTG | 231 |
| #26 | TAGCTGCTGTTGTAGGGTAGGTTGGGTA | 232 |
| #27 | GCCTAGTCCGCGGACGAACTGTGAAGCAC | 233 |
| #28 | GTGACTACTCTCACTCTATGGAACGGTCA | 234 |
| #29 | CGATCGTGGTAGGGTAGGTTGGTGTCAAT | 235 |
| #31 | GCTTATCGGTAGGTGGATGGGCTACTTT | 236 |
| #33 | GCCTTTAGTTGGGGTAGGTGGGTTGGGA | 237 |
| #35 | GCGAGTGGTAGGAGTAGGTTGGAGCCGTA | 238 |
| #36 | GTGAATAGGTAGGTCGGATAGGCTACGGT | 239 |

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TABLE XV. (CONTINUED)

11TH ROUND 60N SEQUENCES

SEQ ID NO:

5'AGATGCTGTGAGCATGCT (60N) GTAGCTAACTGCTTTGTGACGGG-3'

240

CLONE (60N)

| | | |
|-----|--|-----|
| #1 | GCAAAAGCCGGAAATCCCAAGTGTATGCTGAGGGTTGGGGATTTGAAATCCCTGTGGAC | 241 |
| #2 | GACCGGCCAGGGAAGTGGCAGCAGGATGCGTTAGTGTAGGCGCTGCAACTCAGGATTG | 242 |
| #3 | AGCTGTCTCTGTCGCGCTGTGTGAGGGTTGATGGGTGGGTAGGCTAGTCCCATGGCGA | 243 |
| #4 | CTGCGGGTGGACGAGCGGTGTAGGCGAGGTGTGAGTCTGATCTCACGGGCTGGGCA | 244 |
| #6 | TGCTGCTAGCTCTAGTGAAGTATGCGCGGGTAGTGTGGTTGGGGTGGATGCAAG | 245 |
| #7 | GCGCGGTTGGTGTATGCGGCACTGTGTGGCGGAGAGGCTAGGATGCTATGATGCC | 246 |
| #8 | AAGGCTGGAAGCCGGTTGGTTGCGGGGGTAGGCTAGGTGTGATGATGCTACCCACG | 247 |
| #9 | CCGTGCATCAACCGTCCGACCGTGTGTTGCTGTGTAGGGGAGGATGGACCCAGGAGTGG | 248 |
| #10 | AGCCGATGTTCCGTTGGATCTCGGATTTGGTAGGCGAGTTGGGCTCGGATGAGCTCGGA | 249 |
| #11 | TGAGCAGGTGTAGGTTAGGTTGGGTTGCTGCTGAGGCTCTGATCACCGCGGGTGAAG | 250 |
| #12 | GCGAGTGCCTCTTCTGCAAGGTGTGTGCGGAGAGGGTAGGTGTGGATGATGCCGGA | 251 |
| #13 | CTAGCGGCTGTAGGGGAGGTGGGAGTGTGACTCCGCTGGGCGTGAATTCGTGCAAGG | 252 |
| #14 | CTGCGGTTGGACGAGCGGTGTAGGCGAGTTGGAGTCTGATCTCACGGGCGCGGCA | 253 |
| #15 | GCAAGTGGGAGCACGCGGCGCTAGGTTAGGTGTGGATGATCCGGGCAAGCGGTGCGACTT | 254 |
| #16 | GGAAGCTGGGCGACGCTAGGATAGGATGGGCGAGTGGTAGGGCGGTTTCCTGTGCA | 255 |

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TABLE XV. (CONTINUED)

| | | SEQ ID NO: |
|---------|---|------------|
| #18 | CTTTGGAGACAGTCCGTGTTAGGGCAAGTTGGGGTGACTTCGTGGAAGAACGAGACGGT | 256 |
| #19 | GATGGATAACACGTGGCCGGGAGCGTGGTAAGGTAGGATGTTCTGATTCGCCAGGTG | 257 |
| #20 | CGAGCCGGGTATGTTGGGATGGGGCGTAGGACAAGGCAAGTCCGGTGTAGCCGTGG | 258 |
| #21 | GCAAGCCTTCGGTGTGAGTGTAGGTAGGTCCTTGGTTGGGTCTGTCTCCACTGTTTC | 259 |
| #22 | GGCTCGCAGAGGTAGCGTTGGTAAGGTACGTTGGCTCTGAGGAGCCCGCCCTGTCCTG | 260 |
| #24 | CCTGTGAGGGAGCGGGAGGAGTGAGGTTGGCCGTGAGTCCAGGGTGGTAGGCCACTCC | 261 |
| #25 | GACGGGTGACGCGCGGAGCGTGGTAGGGAAAGTTGGGGTCTTCAGCCCTGTGTTGGGCC | 262 |
| #26 | CAGCAATGAGGGCTGGCGGAGTGTGGTAGGGTAGGTTGGTGTGGAAGGAGCACGGTGGT | 263 |
| #27, 32 | GGCGTCCGATGATTCAGGTCGTGGTAGGCATTGAGGGATGGGGTCTGTGGACTGGCCT | 264 |
| #28 | GCAGTAGGGAGCATGCGGGCTAGGGTAGGTTGGATGATGCGGGCAGGGCGTGGCACTT | 265 |
| #29 | GATTGCAATCACTCTGGCGGAGTGTGAGGGAGGTTGGGGCGGTAGGGCCGTAGCCAG | 266 |
| #30 | GAAGCOTTTGGTAGGGTGTGTTGGGCTCGGTGAGGTCTGCGAAGCAGGGAGTGTGCG | 267 |
| #31 | GGAACCGCGAGGGCGCTAGGGTTGAGGGCTTGGCCGATGTGTAGGCACGGACTCGGAT | 268 |
| #33 | TGTTTCGAGTTGGCGGCAAGTGTAGGATCAGGGATGCGAGCCGAAAGATGTGTCGCCAC | 269 |
| #35 | CGGTTAGTCGAGGTTCCGCTAGGCCGTGGTAGGGTAGGTTGGGGCCCTGAGCGGGCG | 270 |
| #36 | TGCTGTCGCTGTTTCGAGCGGCTGTGAGGGAGGTTGGGCATCGTAGGATGTGGCCCG | 271 |

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TABLE XVI. STRUCTURE AND DISSOCIATION CONSTANTS (K_d's) FOR A REPRESENTATIVE SET OF HIGH-AFFINITY DNA LIGANDS TO THROMBIN

| | | | SEQ ID NO: |
|-----------|----------------|---|------------|
| 30N3 | #6 | 5' AGATGCCTGTGAGCATGCT ACACCCGTGTTAGGTA GGATGGGTGGTC GTAGCTAACTGCTTTGTCGACGGG 3' | 272 |
| | #8 | AGATGCCTGTGAGCATGCT GTGAATAGGTAGGGTC GGATGGCTACGGT GTAGCTAACTGCTTTGTCGACGGG | 273 |
| | #16 | AGATGCCTGTGAGCATGCT GCCGCTACGAGCGGTAGGTGT GGATGCTGCC GTAGCTAACTGCTTTGTCGACGGG | 274 |
| | #14 | AGATGCCTGTGAGCATGCT GTTGTGTTAGGGTTAGGATGGTAGCGGTT GTAGCTAACTGCTTTGTCGACGGG | 275 |
| | #35 | AGATGCCTGTGAGCATGCT GGGAGTGTAGGAGTAGGTTGG AGCCGTA GTAGCTAACTGCTTTGTCGACGGG | 276 |
| 60N3 | #7 | AGATGCCTGTGAGCATGCT GGGCGCTTGTGTAGTGGCCACTGTGTTGGCGGAGAGGCTAGGAGTGATGATGCC GTAGCTAACTGCTTTGTCGACGGG | 277 |
| | #18 | AGATGCCTGTGAGCATGCT CTTTGGAGA...CAGTCCGTGTTAGG...GCAAGTTGGGTGACTTCGTGGAAGAGCGAGACGGT GTAGCTAACTGCTTTGTCGA | 278 |
| | #18(38) | CAGTCCGTGTTAGG...GCAAGTTGGGTGACTTCGTGGA | 279 |
| | #27 | AGATGCCTGTGAGCATGCT GGCCTCCGATGATTCAGGTCGTGTAGGCATTGAGGGATGCGGTCCT...GTGGGACTGGCCT GTAGCTAACTGCTTTGTCGACGGG | 280 |
| Ligand | K _d | | |
| 30-6 | 1.2 nM | | |
| 30-8 | 0.4 nM | | |
| 30-14 | 1.0 nM | | |
| 30-16 | 9.4 nM | | |
| 30-35 | 1.4 nM | | |
| 60-7 | 2.5 nM | | |
| 60-18 | 0.92 nM | | |
| 60-18(38) | 1.9 nM | | |
| 60-27 | 0.96 nM | | |

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TABLE XVII. FAMILY 1 RNA LIGANDS TO bFGF.

| | SEQ ID NO: |
|--|------------|
| 4A gggagcucagaauaaacgcucaaaUGCUAUUCCGCUAACUCGGCGUCCUACCUucgacaugaggcccggauccggc | 281 |
| 5A gggagcucagaauaaacgcucaaaAUCUCCUCCCGUCGAAGCUAACUCGGCCACUucgacaugaggcccggauccggc | 282 |
| 7A gggagcucagaauaaacgcucaaaUCGGCGAGCUAACCAAGACACUCCGUGCACUucgacaugaggcccggauccggc | 283 |
| 10A gggagcucagaauaaacgcucaaaGUAGCACUAUCGGCCUAACCCGGUAGCUCCUucgacaugaggcccggauccggc | 284 |
| 13A gggagcucagaauaaacgcucaaaACCGCGGCCUCCGAAGCUAACCAAGGACACUucgacaugaggcccggauccggc | 285 |
| 14A gggagcucagaauaaacgcucaaaUGGGUGCUAACCAAGGACACCCACGCUUucgacaugaggcccggauccggc | 286 |
| 16A gggagcucagaauaaacgcucaaaCAGCACAGCUAACCAAGCCACUUGGCCUucgacaugaggcccggauccggc | 287 |
| 18A gggagcucagaauaaacgcucaaaCUGCGUGGUAUAACCAUGGCCUUGGCCUucgacaugaggcccggauccggc | 288 |
| 21A gggagcucagaauaaacgcucaaaUGGGUGCUAACCAAGGCCACACCCUGCGUUCUucgacaugaggcccggauccggc | 289 |
| 25A gggagcucagaauaaacgcucaaaCUAGGUGCUAUCCAGGACUCUCCUGGUCUucgacaugaggcccggauccggc | 290 |
| 29A gggagcucagaauaaacgcucaaaUGCUAUUCCGCUAGCUCGGCGUCCUACCUucgacaugaggcccggauccggc | 291 |
| 38A gggagcucagaauaaacgcucaaaAGCUAUUCCGCGCAACCCGGCGUCCCGACUucgacaugaggcccggauccggc | 292 |
| 39A gggagcucagaauaaacgcucaaaACCAAGCUGCGUGCAACCGCACUUGCCUGGUCUucgacaugaggcccggauccggc | 293 |
| 56A gggagcucagaauaaacgcucaaaCAGGCCCGUCCGUAAGCUAACCUUGGACCCUucgacaugaggcccggauccggc | 294 |
| 61A gggagcucagaauaaacgcucaaaUGGGUGCUAACCAAGCACACACUACGCUUucgacaugaggcccggauccggc | 295 |

* Arrows indicate the double stranded (stem) regions that flank the conserved loop.
Lower case symbols indicate nucleotides in the constant region.

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TABLE XVIII. FAMILY 2 RNA LIGANDS TO bFGF.

| | SEQ ID NO: |
|---|------------|
| 11A gggagcucagaauaaacgcucaaaGGGUAAACGUUGU--GACAAGUACAUCUCCGUCUucgacaugaggcccggauccggc | 296 |
| 12A gggagcucagaauaaacgcucaaaGGGGCAACGCUACA-GACAAGUGCAUCCAAACUucgacaugaggcccggauccggc | 297 |
| 26A gggagcucagaauaaacgcucaaaCUCAAGAGGCAACGUUAU--GGCAAGCACUucgacaugaggcccggauccggc | 298 |
| 27A gggagcucagaauaaacgcucaaaCCUCUCCGAAGACAACGCUUGU--GACAAGA-CAUucgacaugaggcccggauccggc | 299 |
| 47A gggagcucagaauaaacgcucaaaAGUGGGAAACGCUACUUGACAAGA-CAACACUucgacaugaggcccggauccggc | 300 |
| 65A gggagcucagaauaaacgcucaaaGGCUACGCUAAU-GACAAGUGCAUUGGGUGUucgacaugaggcccggauccggc | 301 |
| 1B gggagaugccugucgagcaugcugCUCUGGUAAACGCAAU--GUCAAGUGCAUUGAGUAGCUaaacagcuuugucgacggg | 302 |
| 2B gggagaugccugucgagcaugcugAGCCCGAGGUAAACGGAAC--GGCAGACCAUUGUAGCUaaacagcuuugucgacggg | 303 |
| 6B gggagaugccugucgagcaugcugACGAGCUUCGUAAACGCUAUC-GACAAGUGCAUUGAGCUaaacagcuuugucgacggg | 304 |
| 8B gggagaugccugucgagcaugcugAAGGGGAAACGUUGA--GUCCGUACACCCUGUAGCUaaacagcuuugucgacggg | 305 |
| 9B gggagaugccugucgagcaugcugAGGGUAAACGUACU--GGCAAGUCACUUCAGCUAGCUaaacagcuuugucgacggg | 306 |
| 11B gggagaugccugucgagcaugcugGAGGUAAACGUAC--GACAAGACCAUCCAAACUUGUAGCUaaacagcuuugucgacggg | 307 |
| 12B gggagaugccugucgagcaugcugAGGUAAACGCUA--GUCAAGUGCAUCCGACUUGUAGCUaaacagcuuugucgacggg | 308 |

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TABLE XVIII. (CONTINUED)

| | | SEQ ID NO: |
|-----|--|------------------|
| 13B | gggagauccugucgagcaugcugGGGAAACGCUAUC-GACGAGUGCA <u>CCCGGC</u> guagcuaaacagcuuugucgacggg | 309 |
| 14B | gggagauccugucgagcaugcugCCAGGGGUAACGUUGG--GUCAAGCACA <u>CCUC</u> guagcuaaacagcuuugucgacggg | 310 |
| 15B | gggagauccugucgagcaugcug <u>UCGCG</u> GUAACGUUU--GGCAAGG-CA <u>CCCGA</u> Cguagcuaaacagcuuugucgacggg | 311 |
| 19B | gggagauccugucgagcaugcugGGUAAACGUGUG-GACAAGUGCA <u>CCAGCUGC</u> guagcuaaacagcuuugucgacggg | 312 |
| 22B | gggagauccugucgagcaugcugAGGGUAAACGUACU--GGCAAGCUCA <u>CCUCAGC</u> guagcuaaacagcuuugucgacggg | 313 |
| 28B | gggagauccugucgagcaugcugAGGGUAAACGUAA--GUCAAGA-CA <u>CCUCA</u> AGguagcuaaacagcuuugucgacggg | 314 |
| 29B | gggagauccugucgagcaugcugGGGUAACGCAU--GGCAAGA-CA <u>CCAGC</u> CCCguagcuaaacagcuuugucgacggg | 315 |
| 36B | gggagauccugucgagcaugcugGAGGAAACGUACC--GUCCAGC-CA <u>CCCAU</u> Gguagcuaaacagcuuugucgacggg | 316 |
| 38B | gggagauccugucgagcaugcugAGGGUAAACGUGA--GUCAAGUGCA <u>CCGACA</u> Uguagcuaaacagcuuugucgacggg | 317 |
| 40B | gggagauccugucgagcaugcugGGGUAACGUGU--GACAAGAUCA <u>CCAGU</u> UUGguagcuaaacagcuuugucgacggg | 318 |
| 49B | gggagauccugucgagcaugcugCACAGGGCAACGUGCU-GACAAGUGCA <u>CCU</u> guagcuaaacagcuuugucgacggg | 319 |

* Arrows indicate the double stranded (stem) regions that flank the conserved loop.
Lower Case symbols indicate nucleotides in constant region.

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TABLE XIX. OLIGONUCLEOTIDES USED IN SELEX EXPERIMENTS
1, 2 AND 3 TO SELECT DNA LIGANDS TO bFGF

EXPERIMENT 1

| | | SEQ ID NO: |
|------|---|------------|
| 5p2 | ATCCGCCTGATTAGCGATACT | 321 |
| 40N2 | ATCCGCCTGATTAGCGATACT (40N) ACTTGAGCAAAATCACCTGCAGGGG | 322 |
| 3p2 | TGAACCTCGTTTATAGTGGACGTCCCCJJJ | 323 |

EXPERIMENT 2

| | | SEQ ID NO: |
|--------|--|------------|
| 5pBH1 | CTACCTACGATCTGACTAGC | 324 |
| 40NBH1 | CTACCTACGATCTGACTAGC (40N) TAGCTTACTCTCATGTATTCC | 325 |
| 3pBH1 | ATCGAATGAGAGTACATAAGGJAJA | 326 |

EXPERIMENT 3

| | | SEQ ID NO: |
|----------|--|------------|
| 5p7.1PS | GGGAGGACGATGCGG | 327 |
| 30N7.1PS | GGGAGGACGATGCGG (30N) CAGACGACGACGGGGA | 328 |
| 3p7.1PS | GTCTGCTGCTGCCCTJAJA | 329 |

J = BIOTIN

HEXAGENIFORMER TABLE 19-8AM

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TABLE XX. AFFINITY OF DNA LIGANDS TO bFGF AFTER EACH ROUND OF SELEX

| Experiment 3 DNA SELEX | | | | | |
|------------------------|-----------------|--|-----------|----------|--------|
| Round | % Bound to bFGF | % Bound to Nitrocellulose (Background) | [bFGF] nM | [DNA] nM | Kd nM |
| 0 | 10 | 59 | 500 | 1000 | ~300nM |
| 1 | 4.8 | 14.5 | 250 | 1000 | |
| 2 | 5.9 | 32.5 | 250 | 1000 | |
| 3 | 5 | 8.9 | 100 | 500 | |
| 4 | 6 | 89 | 100 | 500 | |
| 5 | 1.1 | 19.2 | 33 | 167 | |
| 6 | 2.1 | 9.7 | 50 | 250 | |
| 7 | 2.8 | 3.2 | 33 | 167 | |
| 8 | 1.7 | 5.4 | 20 | 100 | 28 nM |
| 9 | 2.5 | 10.8 | 1 | 5 | |
| 10 | 1.6 | 6.9 | 1 | 5 | 2.5 nM |
| 11 | 1.1 | 7 | 1 | 5 | 4 nM |

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TABLE XXI.

FAMILY 1

ALIGNED SEQUENCE GROUP: 30 SEQS, 0.52 AVG. IDENTITY

EXPERIMENT 1 Sequences

| | | | | SEQ ID NO: |
|------------|---------------------------------|---------------------|--|------------|
| D3 | * ATCCGCTGATTAGCGATACTgtgcgatta | ggggctatgcaaat | cgcactatcagaaggctACTTGAGCAAAATCACCTGCAGGGG | 330 |
| D10 | * ATCCGCTGATTAGCGATACTaaggcc | agggctatgcaaat | cgccgcgcctatggccattACTTGAGCAAAATCACCTGCAGGGG | 331 |
| D12 | * ATCCGCTGATTAGCGATACTaggcc | agggctatgcaaat | cgccgcgcctatggccattACTTGAGCAAAATCACCTGCAGGGG | 332 |
| D22 | ATCCGCTGATTAGCGATACTcggc | agggctatgcaaat | cgccgcgcctatggccattGACTTGAGCAAAATCACCTGCAGGGG | 333 |
| D8 | ATCCGCTGATTAGCGATACTa | ggggctgtgcagac | catggcgaccatcgggatccgtgctACTTGAGCAAAATCACCTGCAGGGG | 334 |
| D42 | ATCCGCTGATTAGCGATACTa | ggggctgtgcagac | catggcgaccatcgggatccgtgctACTTGAGCAAAATCACCTGCAGGGG | 335 |
| D5 | ATCCGCTGATTAGCGATACTgctctc | ggggctttgcaaaa | atcngtagacctacgaggcagACTTGAGCAAAATCACCTGCAGGGG | 336 |
| D19 | * ATCCGCTGATTAGCGATACTgctctc | ggggctttgcaaaa | tctgataactcgtactACTTGAGCAAAATCACCTGCAGGGG | 337 |
| D36 | ATCCGCTGATTAGCGATACTcaa | ggggctttgcaaaa | tgacaaacctaaagcttgacactACTTGAGCAAAATCACCTGCAGGGG | 338 |
| D43 | ATCCGCTGATTAGCGATACTagt | ggggctatgcaaat | tatcgctagtggctgatactacACTTGAGCAAAATCACCTGCAGGGG | 339 |
| Consensus | | RGGGCTNTGCAAA | | 340 |
| Truncation | (D12t2) | AGGCC AGGGCTATGCAAA | CGCGCGCCTATGGCC | 341 |

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EXPERIMENT 2 Sequences

| | | | | |
|-----------|-----------------------|------------------|---|-----|
| b22 | CTACCTACGATCTGACTA | GCagggctttgtaaac | atggactacgtacactatgcaggcaatTAGCTTACTCTCATGTAFPTCC | 342 |
| b26 | CTACCTACGATCTGACTA | gcggggctttgcaaaa | aacgagttgtagttctacgcaatTAGCTTACTCTCATGTAFPTCC | 343 |
| b28 | CTACCTACGATCTGACTA | GCagggctttgtaaac | atggactacgtacactatgcaggcaatTAGCTTACTCTCATGTAFPTCC | 344 |
| b32 | CTACCTACGATCTGACTA | GCagggctttgtaaac | atggactacgtacactatgcaggcaatTAGCTTACTCTCATGTAFPTCC | 345 |
| b5 | CTACCTACGATCTGACTA | GCgggctctgcaaa | tctgaaatgaccacggcagtcgctTAGCTTACTCTCATGTAFPTCC | 346 |
| b7 | CTACCTACGATCTGACTA | GCagggctgtgtaaac | tgggtcTAGCTTACTCTCATGTAFPTCC | 347 |
| b13 | CTACCTACGATCTGACTA | GCagggctttgtaaac | atggactacgtacactatgcaggTAGCTTACTCTCATGTAFPTCC | 348 |
| b14 | CTACCTACGATCTGACTAGCg | gcggggctttgcaaaa | tcgacatactcagactTAGCTTACTCTCATGTAFPTCC | 349 |
| b15 | CTACCTACGATCTGACTA | GCagggctttgtaaac | atggactacgtacactatgcaggTAGCTTACTCTCATGTAFPTCC | 350 |
| Consensus | | CGGGGCTNTGAAAA | | 351 |

* Molecules tested for affinity to bFGF

TABLE XXI. (CONTINUED)

FAMILY 1 (CONTINUED)
EXPERIMENT 3 Sequences

| | | | SEQ ID NO: |
|---------------------|---|--|------------|
| M17 | * | GGGAGGACGATGC Ggggggctttgcaaaa attgttaaatctacccCAGACGACGACGGGA | 352 |
| M19 | * | GGGAGGACGAT GC0gggctatgtaaat tactgtctactacgcacCAGACGACGACGGGA | 353 |
| M23 | | GGGAGGACGATGCG0 ggggggctctgtaaaag tctttcaactaccacCAGACGACGACGGGA | 354 |
| M24 | | GGGAGGACGATG C0ggggctctgcaaaag tgaatccccactaccCAGACGACGACGGGA | 355 |
| M210 | | GGGAGGACGATGC G0ggggctctgcaaaag tttcgttaactactcCAGACGACGACGGGA | 356 |
| M217 | | GGGAGGACGATGCGgggctacgta cgggggctttgtaaaa ccccgCAGACGACGACGGGA | 357 |
| M222 | | GGGAGGACGATG C0ggggctatgcaaat tttccaaactactgcacCAGACGACGACGGGA | 358 |
| M225 | * | GGGAGGACGATGCGgggctacgta cgggggctttgtaaaa ccccgCAGACGACGACGGGA | 359 |
| M235 | * | GGGAGGACGAT GC0gggctctgcaaaag gacacaggtcctacgcacCAGACGACGACGGGA | 360 |
| M236 | | GGGAGGACGAT GC0gggctctgcaaat cctcctcgggaggtacgCAGACGACGACGGGA | 361 |
| M242 | | GGGAGGACGAT GC0gggctttgtaaaa tctcatctgagactacgCAGACGACGACGGGA | 362 |
| Consensus | | SSGGGCTTTGCAAA | 363 |
| Truncation (M225t3) | | GCGGGCTTA0TAC C0GGGCTTTGTA AAA CCCCC | 364 |
| Truncation (m19t2) | | G C0GGGCTATGTAAAT TACTGCTGTACTACGATC | 365 |

* Molecules tested for affinity to bPGF

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TABLE XXI. (CONTINUED)

FAMILY 2

ALIGNED SEQUENCE GROUP: 24 SEQS, 0.42 AVG. IDENTITY

EXPERIMENT 1 Sequences

| | | | SEQ ID NO: |
|-----|---|---|------------|
| d2 | | ATCCGCTGATTAGCGATACTgtctc cgcaggagcgtagtcgacacagccccaaagtgtatCTTGAGCAAAATCACCTGCAGGGG | 366 |
| d14 | | ATCCGCTGATTAGCGATACTgaccaagactg atgcgtcgccctccgatcgccagttacccACTTGAGCAAAATCACCTGCAGGGG | 367 |
| d15 | | ATCCGCTGATTAGCGATACTgaccaagactg atgcgtcgccctccgatagccagttactcACTTGAGCAAAATCACCTGCAGGGG | 368 |
| d27 | | ATCCGCTGATTAGCGATACTttaacacctcaactggcaacgtcccgaaagctcccgagtcACTTGAGCAAAATCACCTGCAGGGG | 369 |
| d29 | | ATCCGCTGATTAGCGATACTgaccaagactg atgcgtcgccctccgatagctgttaccACTTGAGCAAAATCACCTGCAGGGG | 370 |
| d30 | | ATCCGCTGATTAGCGATACTttaacacctcaactggcaacgtcccgaaagctcccgagtcACTTGAGCAAAATCACCTGCAGGGG | 371 |
| d34 | | ATCCGCTGATTAGCGATACTgaccaagactg atgcgtcgccctccgatagccagttacccACTTGAGCAAAATCACCTGCAGGGG | 372 |
| d37 | * | ATCCGCTGATTAGCGATACTgaccaagactg atgcgtcgccctccgatagccagttacccACTTGAGCAAAATCACCTGCAGGGG | 373 |
| d40 | | ATCCGCTGATTAGCGATACTgtctc cgcaggagcgtagtcgacacagccccaaagggaACTTGAGCAAAATCACCTGCAGGGG | 374 |
| d44 | * | ATCCGCTGATTAGCGATACTgaccaagactg atgcgtcgccctccgatagccagttacccACTTGAGCAAAATCACCTGCAGGGG | 375 |
| d46 | * | ATCCGCTGATTAGCGATACTaacaagctctg ctgcacccctcgtactaa cgttaccagctACTTGAGCAAAATCACCTGCAGGGG | 376 |
| d50 | | ATCCGCTGATTAGCGATACTtggtgctcggggagaaattggctacggacccggttacctacACTTGAGCAAAATCACCTGCAGGGG | 377 |

EXPERIMENT 2 Sequences

| | | | |
|-----|--|--|-----|
| b19 | | CTACCTACGATCTGACTAGctggaggcgtt cctggacagttctcgagagTAGCTTACTCTCATGTAFPTCC | 378 |
| b23 | | CTACCTACGATCTGACTAGctggaggcgtt cctggacagttctcgagagctctccacaaTAGCTTACTCTCATGTAFPTCC | 379 |
| b29 | | CTACCTACGATCTGACTAGctggaggcgtt cctggacagttctcgagagctctccacaaTAGCTTACTCTCATGTAFPTCC | 380 |
| b33 | | CTACCTACGATCTGACTAGctggaggcgtt cctggacagttctcgagagctctccacaaTAGCTTACTCTCATGTAFPTCC | 381 |
| b25 | | CTACCTACGATCTGACTAGctggaggcgtt ttttaacgccacagtgaaagcgggttgacttatTAGCTTACTCTCATGTAFPTCC | 382 |
| b3 | | CTACCTACGATCTGACTAGctggaggcgtt cctggacagttctcgagagTAGCTTACTCTCATGTAFPTCC | 383 |

EXPERIMENT 3 Sequences

| | | | |
|-----------------------|---|--|-----|
| m2 | | GGGAGGACGATGCGgacgatagacgtcaggaatcttttagtccacCAGACGACGACGGGA | 384 |
| m215 | | GGGAGGACGATGCGgacgatagacgtcaggaatcttttagtccacCAGACGACGACGGGA | 385 |
| m228 | | GGGAGGACGATGCGgacgatagacgtcaggaatcttttagtccacCAGACGACGACGGGA | 386 |
| m234 | * | GGGAGGACGATGCGgacgatagacgtcaggaatcttttagtccacCAGACGACGACGGGA | 387 |
| m237 | | GGGAGGACGATGCGgacgatagacgtcaggaatcttttagtccacCAGACGACGACGGGA | 388 |
| m250 | | GGGAGGACGATGCGgacgatagacgtcaggaatcttttagtccacCAGACGACGACGGGA | 389 |
| 43 Consensus | | CGAGGAC- YTTARYGCCCRG | 390 |
| 44 Truncation (234t2) | | CGAGGAC-CTTTAGCGCCACAGTT | 391 |

* Molecules tested for affinity to bPGF

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TABLE XXI. (CONTINUED)

FAMILY 3

ALIGNED SEQUENCE GROUP: 18 SEQS, 0.42 AVG. IDENTITY

| EXPERIMENT 1 Sequences | SEQ ID NO: |
|--|------------|
| d7 ATCCGCTGATTAGCGATACTtgagtgcatcgctcacctcgacctaaggctccagttggaatACTTGAGCAAAATCACCTGCAGGGG | 392 |
| d13 ATCCGCTGATTAGCGATACTgcaaaaggcaacttggcctgggttaataggttcgctgccacatACTTGAGCAAAATCACCTGCAGGGG | 393 |
| d17 ATCCGCTGATTAGCGATACTacaaggcaacccgggtacatagggttcgttaaaactgacacgACTTGAGCAAAATCACCTGCAGGGG | 394 |
| d21 ATCCGCTGATTAGCGATACTtgactgt gcggtcacctcggtcgaaaacccagtaaaactcaACTTGAGCAAAATCACCTGCAGGGG | 395 |
| d25 ATCCGCTGATTAGCGATACTtgactgt gcggtcacctcggttgaaaacccagtaaaactcaACTTGAGCAAAATCACCTGCAGGGG | 396 |
| d32 ATCCGCTGATTAGCGATACTcagcatggcaagatctcggcgcggtgtatccggtatcgACTTGAGCAAAATCACCTGCAGGGG | 397 |
| d41 ATCCGCTGATTAGCGATACTgcaaaaggcaacttggcctgggttaataggttcgctgccacatACTTGAGCAAAATCACCTGCAGGGG | 398 |
| EXPERIMENT 2 Sequences | |
| b18 CTACCTACGATCTGACTAGTaccaccatgtgcagggtttcgagccaaactgggtcggtTAGCTTACTCTCATGTAFPTCC | 399 |
| b31 CTACCTACGATCTGACTAGCctcactgactgtcggtcacctcgactgaagtcaggtttTAGCTTACTCTCATGTAFPTCC | 400 |
| b35 CTACCTACGATCTGACTAGCcaactctgggaacacccagcaaggtccctcgctcacttgTAGCTTACTCTCATGTAFPTCC | 401 |
| b1 CTACCTACGATCTGACTAGCactgcacacggttatggaggtTAGCTTACTCTCATGTAFPTCC | 402 |
| b16 CTACCTACGATCTGACTAGCactgagtagccagagtgccctcgccgctgaatcggaaccaTAGCTTACTCTCATGTAFPTCC | 403 |
| EXPERIMENT 3 Sequences | |
| m202 GGGAGGACGATGCGGtcgctcggtataaggcctagggtttcggttacCAGACGACGACGGGGA | 404 |
| m203 GGGAGGACGATGCGGcctcggtcggtattcttgccactctcagtaaCAGACGACGACGGGGA | 405 |
| m208 GGGAGGACGATGCGGcgcgcggtttgggacataggggcaacacataCAGACGACGACGGGGA | 406 |
| m219 GGGAGGACGATGCGGcagcgacgcggttacaaggcatagggttaCAGACGACGACGGGGA | 407 |
| m227 GGGAGGACGATGCGGcgacagtcacggtgcaaggcctgggtcCAGACGACGACGGGGA | 408 |
| m233 GGGAGGACGATGCGGcaggcggttggtacaagtcggactccctcCAGACGACGACGGGGA | 409 |

* Molecules tested for affinity to bPGP

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TABLE XXI. (CONTINUED)

FAMILY 4

ALIGNED SEQUENCE GROUP: 13 SEQS, 0.47 AVG. IDENTITY

| EXPERIMENT 1 Sequences | SEQ ID NO: |
|--|------------|
| d33 ATCCGCTGATTAGCGATACTtgagcaactcggttcacggcagatcggttaatccccACTTGAGCAAAATCACCTGCAGGGG | 410 |
| d49 ATCCGCTGATTAGCGATACTagagcaactcggttcacggcagatcggttaatccccACTTGAGCAAAATCACCTGCAGGGG | 411 |
| EXPERIMENT 2 Sequences | |
| b17 CTACCTACGATCTGACTAGCaacggatgttaacacctaccatgcagggtgcgcaccaaacagTAGCTTACTCTCATGTAFPTCC | 412 |
| b20 CTACCTACGATCTGACTAGCatacctgaccataaggtccgaagat ctcggagtagctatTAGCTTACTCTCATGTAFPTCC | 413 |
| b8 CTACCTACGATCTGACTAGCcaactgcataaggataccgactccgattgtatgtTAGCTTACTCTCATGTAFPTCC | 414 |
| b10 CTACCTACGATCTGACTAGCcaactgcataaggataccgactccgattgtatgtcaccTAGCTTACTCTCATGTAFPTCC | 415 |
| EXPERIMENT 3 Sequences | |
| m15 GGGAGGACGATGCGGaggactcgtaaccgcacgggtgacactctggCAGACGACGACGGGGA | 416 |
| m29 GGGAGGACGATGCGGggcgcggagac caggggaattcccacagcgCAGACGACGACGGGGA | 417 |
| m221 GGGAGGACGATGCGGccagctagcggaaagggaagtctcgacgaacatCAGACGACGACGGGGA | 418 |
| m48 GGGAGGACGATGCGGgggggggagcgagacacacgggaatttcaCAGACGACGACGGGGA | 419 |
| m247 GGGAGGACGATGCGGccaggtgggggggatcatcaggggtttgtcgaCAGACGACGACGGGGA | 421 |
| m249 GGGAGGACGATGCGGccagctagcggaaaggaa tct gacgaacatCAGACGACGACGGGGA | 422 |

* Molecules tested for affinity to bPGP

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TABLE XXI. (CONTINUED)

FAMILY 5

ALIGNED SEQUENCE GROUP: 10 SEQS, 0.42 AVG. IDENTITY

EXPERIMENT 1 Sequences

| | | SEQ ID NO: |
|---|---|------------|
| d1 * | ATCCGCTGATTAGCGATACTacacccaacccccaagatttttagagcaactcggcgcaacACTTGAGCAAAATCACCTGCAGGGG | 423 |
| d9 * | | |
| ATCCGCTGATTAGCGATACTegaagagtaggaggcgatccgctccgtatcaggtcacataggACTTGAGCAAAATCACCTGCAGGGG | | 424 |
| d28 | ATCCGCTGATTAGCGATACTacacccaacccccaagatttttagagcaactcggcgcaacACTTGAGCAAAATCACCTGCAGGGG | 425 |

EXPERIMENT 2 Sequences

| | | |
|-----|---|-----|
| b34 | CTACCTACGATCTGACTAGCcacccaaggttggatgagggtagggtcaagggtcggtatccTAGCTTACTCTCATGTAFTTCC | 426 |
| b2 | CTACCTACGATCTGACTAGCgacgacgtagtccaaagggtcatagtagcgtgtcagtcTAGCTTACTCTCATGTAFTTCC | 427 |

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EXPERIMENT 3 Sequences

| | | |
|--------|---|-----|
| m28 | GGGAGGACGATGCGGacacgggtagtcggaggattcaacttccgccCAGACGACGACGGGA | 428 |
| m207 | GGGAGGACGATGCGGcaggcgacctatatagggtgggtatccccgtacCAGACGACGACGGGA | 429 |
| m224 * | GGGAGGACGATGCGGcaccgaggaataactgacgccaggctggcgCAGACGACGACGGGA | 430 |
| m246 | GGGAGGACGATGCGGcctcagcggatttcttggcgagtaggagcgCAGACGACGACGGGA | 431 |

* Molecules tested for affinity to bFGF

PCT/US95/01458

TABLE XXI. (CONTINUED)

FAMILY 5 (CONTINUED)

ORPHAN SEQUENCES: (46)

EXPERIMENT 1 Sequences

| | | SEQ ID NO: |
|-------|--|------------|
| d20 | ATCCGCTGATTAGCGATACTaaggcaaacacgtgaccgagggttagagggtgggtcctagcACTTGAGCAAAATCACCTGCAGGGG | 432 |
| d31 * | ATCCGCTGATTAGCGATACTacatgacgatccggccgagtggtgggtttcaaggtcoggACTTGAGCAAAATCACCTGCAGGGG | 433 |

EXPERIMENT 2 Sequences

| | | |
|-----|---|-----|
| b4 | CTACCTACGATCTGACTAGCagctagtgcaacttcagtagtaaccgagtggttgggaatcaagTAGCTTACTCTCATGTAFTTCC | 434 |
| b24 | CTACCTACGATCTGACTAGCcotctagtagtcagctcgaggcatgcaagcttaccactatgcgTAGCTTACTCTCATGTAFTTCC | 435 |

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EXPERIMENT 3 Sequences

| | | |
|--------|---|-----|
| m26 | GGGAGGACGATGCGGGGGCTATGCGATACAGTCGCGNTANGCTAGGCGCAGACGACGGGA | 436 |
| m204 | GGGAGGACGATGCGGcctngatgcagcgtcggtaggcnaancgccgaagccnCAGACGACGACGGGA | 437 |
| m206 * | GGGAGGACGATGCGGacctgggtggctgtgcttatgtccccctcatCAGACGACGACGGGA | 438 |
| m209 | GGGAGGACGATGCGGgaggtgggtgtacatctctnagcaagcatCAGACGACGACGGGA | 439 |
| m232 | GGGAGGACGATGCGGcctgtgactgtgcttatgtctccacatCAGACGACGACGGGA | 440 |
| m240 | GGGAGGACGATGCGGctactgtactgcttatgtctgtccccctcgtCAGACGACGACGGGA | 441 |
| m241 | GGGAGGACGATGCGGggggagtcacatcacccacccactcctcgtCAGACGACGACGGGA | 442 |

* Molecules tested for affinity to bFGF

HEXAGRAM FIGURES TABLE 21V-RAM

PCT/US95/01458

TABLE XXII.

ISOLATES AND TRUNCATES WITH THE HIGHEST AFFINITY FOR BFGF

| Ligand | K _d nM | SEQ ID NO: |
|--------|-------------------|------------|
| M17 | 6.9 | 352 |
| M19 | 0.3 | 353 |
| m26 | 1.6 | 436 |
| m206 | 1.8 | 438 |
| m224 | 1.5 | 430 |
| M225 | 0.1 | 459 |
| m234 | 0.7 | 487 |
| M235 | 0.2 | 460 |
| D12 | 0.3 | 432 |
| D19 | 0.1 | 437 |
| D3 | 0.3 | 430 |
| D10 | 0.3 | 431 |

| Truncations | K _d nM | SEQ ID NO: |
|-------------|-------------------|------------|
| M225T3 | 0.7 | 364 |
| M19T2 | 1 | 365 |
| M235T2 | 1 | 420 |
| D12T2 | 1 | 341 |
| m234T2 | 6 | 391 |
| M225T3GC | 0.2 | 443 |

HEXAGONFIGURESTABLE XXV-EAM

SEQUENCE LISTING

- (1) GENERAL INFORMATION:
- (i) APPLICANT: Gold, Larry
Janic, Nehojas
Tasset, Diane
- (ii) TITLE OF INVENTION: HIGH-AFFINITY LIGANDS OF BASIC FIBROBLAST GROWTH FACTOR AND THROMBIN
- (iii) NUMBER OF SEQUENCES: 445
- (iv) CORRESPONDENCE ADDRESSES:
- (A) ADDRESSEE: Swanson & Bratschun, L.L.C.
(B) STREET: 8400 E. Prentice Avenue, Suite 200
(C) CITY: Englewood
(D) STATE: Colorado
(E) COUNTRY: USA
(F) ZIP: 80111
- (v) COMPUTER READABLE FORM:
- (A) MEDIUM TYPE: Diskette, 3.5 inch, 1.44 MB storage
(B) COMPUTER: IBM compatible
(C) OPERATING SYSTEM: MS-DOS
(D) SOFTWARE: Wordperfect 5.1
- (vi) CURRENT APPLICATION DATA:
- (A) APPLICATION NUMBER:
(B) FILING DATE:
(C) CLASSIFICATION:
- (vii) PRIOR APPLICATION DATA:
- (A) APPLICATION NUMBER: 08/195,005
(B) FILING DATE: 10-FEBRUARY-1994
(C) CLASSIFICATION:
- (viii) PRIOR APPLICATION DATA:
- (A) APPLICATION NUMBER: 08/061,691
(B) FILING DATE: 22-APRIL-1993
(C) CLASSIFICATION:
- (ix) PRIOR APPLICATION DATA:
- (A) APPLICATION NUMBER: 08/219,012
(B) FILING DATE: 28-MARCH-1994
(C) CLASSIFICATION:
- (x) PRIOR APPLICATION DATA:
- (A) APPLICATION NUMBER: 07/973,333
(B) FILING DATE: 11-NOVEMBER-1992
(C) CLASSIFICATION:
- (xi) PRIOR APPLICATION DATA:
- (A) APPLICATION NUMBER: 07/714,131
(B) FILING DATE: 10-JUNE-1991
(C) CLASSIFICATION:

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(vii) PRIOR APPLICATION DATA:

- (A) APPLICATION NUMBER: 07/536,428
 (B) FILING DATE: 11-JUNE-1990
 (C) CLASSIFICATION:

(viii) ATTORNEY/AGENT INFORMATION:

- (A) NAME: Barry J. Swanson
 (B) REGISTRATION NUMBER: 33,215
 (C) REFERENCE/DOCKET NUMBER: NEX07/PCT

(ix) TELECOMMUNICATION INFORMATION:

- (A) TELEPHONE: (303) 793-3333
 (B) TELEFAX: (303) 793-3433

(2) INFORMATION FOR SEQ ID NO:1:

(1) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 77 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

GCGAGCTCCG AAUAAAGCGU CAANNNNNNN NNNNNNNNNN
 NNNNUCAGCA UGAGGCCCGG AUCCGCGC

50

(2) INFORMATION FOR SEQ ID NO:2:

(1) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 48 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

CCGAGCTTA ATACGATCTA CTATAGGAG CTCAGATTA AGCTCGA

48

(2) INFORMATION FOR SEQ ID NO:3:

(1) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 24 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

GCGGATCCG GCGCTCATGT CGAA

24

(2) INFORMATION FOR SEQ ID NO:4:

(1) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 79 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

GGAAGATCC TGGCAGACAT GTGNNNNNNN NNNNNNNNNN
 NNNNGUAGCU AAACGACCTU GUCAGCGG

50

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(2) INFORMATION FOR SEQ ID NO:5:

(1) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 50 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

CCGAGCTT ATACGACTC ACTATAGGGA GATGCTGTG GAGCATGCTG

50

(2) INFORMATION FOR SEQ ID NO:6:

(1) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 25 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

CCGTCGACA AAGCTGTTA GCTAC

25

(2) INFORMATION FOR SEQ ID NO:7:

(1) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 9 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

CTACACGAG

9

(2) INFORMATION FOR SEQ ID NO:8:

(1) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 30 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

UCGUADUCC CUACUCGCG GCUCCUACCU

30

(2) INFORMATION FOR SEQ ID NO:9:

(1) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 30 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

AUUCUCCUCC GUCAAGACUA ACUGGCGCAC

30

(2) INFORMATION FOR SEQ ID NO:10:

(1) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 30 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

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UCGGCGAGCTU AACCAAGACA CUCGCGUCAC

30

(2) INFORMATION FOR SEQ ID NO:11:

(1) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 30 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(X1) SEQUENCE DESCRIPTION: SEQ ID NO:11:
GUAGCAUAT CAGCCUAC CCGUAGCUC

30

(2) INFORMATION FOR SEQ ID NO:12:

(1) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 30 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(X1) SEQUENCE DESCRIPTION: SEQ ID NO:12:
ACCCGCGGCC UCCAGACCUA ACCAGAGCAC

30

(2) INFORMATION FOR SEQ ID NO:13:

(1) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 30 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(X1) SEQUENCE DESCRIPTION: SEQ ID NO:13:
UGGUGUCUA CAGAGACACA CCGAGCGCU

30

(2) INFORMATION FOR SEQ ID NO:14:

(1) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 30 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(X1) SEQUENCE DESCRIPTION: SEQ ID NO:14:
CAGCAGAC UAACCAAGC ACUGGCCCC

30

(2) INFORMATION FOR SEQ ID NO:15:

(1) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 30 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(X1) SEQUENCE DESCRIPTION: SEQ ID NO:15:
CUCGUGUA UAACCAAG CCGUGGACA

30

(2) INFORMATION FOR SEQ ID NO:16:

(1) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 30 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single

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(D) TOPOLOGY: linear

(X1) SEQUENCE DESCRIPTION: SEQ ID NO:16:
UGGUGUCUA ACCAGAGCAC ACCUGCGU

30

(2) INFORMATION FOR SEQ ID NO:17:

(1) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 30 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(X1) SEQUENCE DESCRIPTION: SEQ ID NO:17:
CUAGUGCUA UCCAGAGAC UCCUGGUC

30

(2) INFORMATION FOR SEQ ID NO:18:

(1) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 30 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(X1) SEQUENCE DESCRIPTION: SEQ ID NO:18:
UCGUAGUCU CUAUCGAC GCUCCUACU

30

(2) INFORMATION FOR SEQ ID NO:19:

(1) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 30 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(X1) SEQUENCE DESCRIPTION: SEQ ID NO:19:
ACGUAGUCU CCAACCGAC GCUCCGACC

30

(2) INFORMATION FOR SEQ ID NO:20:

(1) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 29 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(X1) SEQUENCE DESCRIPTION: SEQ ID NO:20:
ACGAGCUGG UGCAACGCA CAUGCCUG

29

(2) INFORMATION FOR SEQ ID NO:21:

(1) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 30 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(X1) SEQUENCE DESCRIPTION: SEQ ID NO:21:
CAGGCCCUU CGUAGCUA CUGGACCU

30

(2) INFORMATION FOR SEQ ID NO:22:

(1) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 30 base pairs

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(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(X1) SEQUENCE DESCRIPTION: SEQ ID NO:22:
UGGUGUCUA CCACCACACA CUCACGCUU

30

(2) INFORMATION FOR SEQ ID NO:23:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 26 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(X1) SEQUENCE DESCRIPTION: SEQ ID NO:23:
RRGHAACG WNGDCAGN NCACY

26

(2) INFORMATION FOR SEQ ID NO:24:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(X1) SEQUENCE DESCRIPTION: SEQ ID NO:24:
GGUAGCUU GUGACAGUA CACUCGCU

30

(2) INFORMATION FOR SEQ ID NO:25:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(X1) SEQUENCE DESCRIPTION: SEQ ID NO:25:
GGGGCAACG UACGACAG UGCACCCAC

30

(2) INFORMATION FOR SEQ ID NO:26:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(X1) SEQUENCE DESCRIPTION: SEQ ID NO:26:
CGUCAGAGG CAACGUAUG GCAAGCACG

30

(2) INFORMATION FOR SEQ ID NO:27:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(X1) SEQUENCE DESCRIPTION: SEQ ID NO:27:
CCUCUCAGG ACAAGCUCU GACAGACAC

30

(2) INFORMATION FOR SEQ ID NO:28:

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(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(X1) SEQUENCE DESCRIPTION: SEQ ID NO:29:
AGUGGAAAC GCUACUCAG ACAGACCCAC

30

(2) INFORMATION FOR SEQ ID NO:30:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(X1) SEQUENCE DESCRIPTION: SEQ ID NO:30:
GGCUCGCUA AUGACAGUG CACUCGCU

30

(2) INFORMATION FOR SEQ ID NO:31:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(X1) SEQUENCE DESCRIPTION: SEQ ID NO:31:
CUCUGUAC GCAUGUCA GUGCACAUCA

30

(2) INFORMATION FOR SEQ ID NO:32:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(X1) SEQUENCE DESCRIPTION: SEQ ID NO:32:
AGCGCAGU AACGACCG CGAGACCAU

30

(2) INFORMATION FOR SEQ ID NO:33:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(X1) SEQUENCE DESCRIPTION: SEQ ID NO:33:
ACGACUCUG UACGCUAC GACAGUCA

30

(2) INFORMATION FOR SEQ ID NO:34:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(X1) SEQUENCE DESCRIPTION: SEQ ID NO:34:
AAGGGAAC GUGAGUCG GUAACCCG

30

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- (2) INFORMATION FOR SEQ ID NO:34:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(x1) SEQUENCE DESCRIPTION: SEQ ID NO:34:
AGGUAACGU ACUGGCAAGC UCACUCCAGC 30
- (2) INFORMATION FOR SEQ ID NO:35:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(x1) SEQUENCE DESCRIPTION: SEQ ID NO:35:
GAGUAACGU AGCAACAAGC CACUCCAGC 30
- (2) INFORMATION FOR SEQ ID NO:36:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(x1) SEQUENCE DESCRIPTION: SEQ ID NO:36:
AGGUAACGU GAGUCAAGU CACUCCAGC 30
- (2) INFORMATION FOR SEQ ID NO:37:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(x1) SEQUENCE DESCRIPTION: SEQ ID NO:37:
GGGAAAGCU AUCGACAGU GCACCCGCA 30
- (2) INFORMATION FOR SEQ ID NO:38:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(x1) SEQUENCE DESCRIPTION: SEQ ID NO:38:
CCGAGGUAU CGUUGGUCA AGCAGACUCC 30
- (2) INFORMATION FOR SEQ ID NO:39:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(x1) SEQUENCE DESCRIPTION: SEQ ID NO:39:

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- UCGAGGUAAC GUUUGGUCA GGCACCCGAC 30
- (2) INFORMATION FOR SEQ ID NO:40:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(x1) SEQUENCE DESCRIPTION: SEQ ID NO:40:
GUUAAGCUG UGCACAAGU CACGAGCUGC 30
- (2) INFORMATION FOR SEQ ID NO:41:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(x1) SEQUENCE DESCRIPTION: SEQ ID NO:41:
AGGUAACGU ACUGGCAAGC UCACUCCAGC 30
- (2) INFORMATION FOR SEQ ID NO:42:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(x1) SEQUENCE DESCRIPTION: SEQ ID NO:42:
AGGUAACGU AUCGACAGU CACUCCAGC 30
- (2) INFORMATION FOR SEQ ID NO:43:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(x1) SEQUENCE DESCRIPTION: SEQ ID NO:43:
GGGAAAGCU UUGGCAAGC ACCGAGCCCC 30
- (2) INFORMATION FOR SEQ ID NO:44:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(x1) SEQUENCE DESCRIPTION: SEQ ID NO:44:
GAGAAAGCU ACCGUGGAGC CACUCCAGC 30
- (2) INFORMATION FOR SEQ ID NO:45:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single

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- (D) TOPOLOGY: linear
(X1) SEQUENCE DESCRIPTION: SEQ ID NO:45:
AGGUAAGCU GAGUAGAGU GACCGACAU 30
- (2) INFORMATION FOR SEQ ID NO:46:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(X1) SEQUENCE DESCRIPTION: SEQ ID NO:46:
GGGUAAGUG UGACAGAGU ACCGAGUUG 30
- (2) INFORMATION FOR SEQ ID NO:47:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(X1) SEQUENCE DESCRIPTION: SEQ ID NO:47:
CACAGGCGCA GCGUGGUGAC AAGUGCAGCU 30
- (2) INFORMATION FOR SEQ ID NO:48:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(X1) SEQUENCE DESCRIPTION: SEQ ID NO:48:
ACGCCAAGUG AGUCAGGAC AGAGCGUCCG 30
- (2) INFORMATION FOR SEQ ID NO:49:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(X1) SEQUENCE DESCRIPTION: SEQ ID NO:49:
CCAGUGAGUC CUGGUAUCC GCAGCGGCGU 30
- (2) INFORMATION FOR SEQ ID NO:50:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(X1) SEQUENCE DESCRIPTION: SEQ ID NO:50:
CUCGAGAGG GCAUAGUGU CGCCGCGCGC 30
- (2) INFORMATION FOR SEQ ID NO:51:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs

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- (B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(X1) SEQUENCE DESCRIPTION: SEQ ID NO:51:
AGUCAGCUG GUCACGCUAC AUGCCUGGCGC 30
- (2) INFORMATION FOR SEQ ID NO:52:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(X1) SEQUENCE DESCRIPTION: SEQ ID NO:52:
UCCAGCGAC GACCCUGGA UUCAGCCAC 30
- (2) INFORMATION FOR SEQ ID NO:53:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(X1) SEQUENCE DESCRIPTION: SEQ ID NO:53:
ACUGAAGCU GACUGAGUAC AGCAGCCUC 30
- (2) INFORMATION FOR SEQ ID NO:54:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(X1) SEQUENCE DESCRIPTION: SEQ ID NO:54:
UUCGCGUGG CCUACAGGC AUGCCGCGA 29
- (2) INFORMATION FOR SEQ ID NO:55:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(X1) SEQUENCE DESCRIPTION: SEQ ID NO:55:
GAUGCAGUG CAUGCCUGC AUAUCUGGUC 30
- (2) INFORMATION FOR SEQ ID NO:56:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(X1) SEQUENCE DESCRIPTION: SEQ ID NO:56:
UUCUGGUGG CCUACAGGC AUGCCGCGA 30
- (2) INFORMATION FOR SEQ ID NO:57:

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- (1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:57:
UGACGACGCU CAUCCGACGA UAUACCTUGG 30
- (2) INFORMATION FOR SEQ ID NO:58:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:58:
GGCACACTCC AACGAGGUA GCUACGGCG 30
- (2) INFORMATION FOR SEQ ID NO:59:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:59:
AGCGAGACCG CAGGAGUAC GCCGACCCG 30
- (2) INFORMATION FOR SEQ ID NO:60:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:60:
ACCGACGCC GACGACCGAU GAGUUCUCGG 30
- (2) INFORMATION FOR SEQ ID NO:61:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:61:
UGCUUUGAAG UCUCCCCCG CUCUGGAGU 30
- (2) INFORMATION FOR SEQ ID NO:62:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:62:
AUGCGAGGA UAUGUGACC ACUUGGGGU 30

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- (2) INFORMATION FOR SEQ ID NO:63:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:63:
ACCGACGCC GACGACCGAU GAGUUCUGG 29
- (2) INFORMATION FOR SEQ ID NO:64:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:64:
AGUCGAGAU CCCGACGCG ACUACAUUG 30
- (2) INFORMATION FOR SEQ ID NO:65:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:65:
AAGUCGGAU GCCACUGGGA CUACGACUGA 30
- (2) INFORMATION FOR SEQ ID NO:66:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:66:
ACUUCACUG CGAUCGAAA UCAUGCCUGG 30
- (2) INFORMATION FOR SEQ ID NO:67:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:67:
AGGCUGGGUC ACCGACGACU GCCCGCCGAC 30
- (2) INFORMATION FOR SEQ ID NO:68:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:68:

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AGCCGACGU AACGACCG CGAGACACU

30

(2) INFORMATION FOR SEQ ID NO:69:

(1) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 30 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(x1) SEQUENCE DESCRIPTION: SEQ ID NO:69:
GCAUGAAGG GAACGUAGU AACGACGCA

30

(2) INFORMATION FOR SEQ ID NO:70:

(1) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 30 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(x1) SEQUENCE DESCRIPTION: SEQ ID NO:70:
GGGUAAGGU GUGACAGUA CACCGGCUU

30

(2) INFORMATION FOR SEQ ID NO:71:

(1) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 30 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(x1) SEQUENCE DESCRIPTION: SEQ ID NO:71:
GGGUAAGGU GUGACAGUA CACCGGCUU

30

(2) INFORMATION FOR SEQ ID NO:72:

(1) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 30 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(x1) SEQUENCE DESCRIPTION: SEQ ID NO:72:
GGGUAAGGU GUGACAGUA CACCGGCUU

30

(2) INFORMATION FOR SEQ ID NO:73:

(1) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 30 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(x1) SEQUENCE DESCRIPTION: SEQ ID NO:73:
GGGUAAGGU GUGACAGUA CACCGGCUU

30

(2) INFORMATION FOR SEQ ID NO:74:

(1) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 30 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single

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(D) TOPOLOGY: linear

(x1) SEQUENCE DESCRIPTION: SEQ ID NO:74:
GGGUAAGGU GUGACAGUA CACCGGCUU

30

(2) INFORMATION FOR SEQ ID NO:75:

(1) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 30 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(x1) SEQUENCE DESCRIPTION: SEQ ID NO:75:
GGGUAAGGU GUGACAGUA CACCGGCUU

30

(2) INFORMATION FOR SEQ ID NO:76:

(1) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 30 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(x1) SEQUENCE DESCRIPTION: SEQ ID NO:76:
CGUCAGAAAG CAACGUATAG GCAAGACAC

30

(2) INFORMATION FOR SEQ ID NO:77:

(1) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 30 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(x1) SEQUENCE DESCRIPTION: SEQ ID NO:77:
GUGACAGUA CGGCUUAC CGGUAAGCUU

30

(2) INFORMATION FOR SEQ ID NO:78:

(1) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 30 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(x1) SEQUENCE DESCRIPTION: SEQ ID NO:78:
ACCCGGGCG UCGAGACUA ACCAGGAC

30

(2) INFORMATION FOR SEQ ID NO:79:

(1) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 30 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(x1) SEQUENCE DESCRIPTION: SEQ ID NO:79:
AGGUAACGU GUGACAGUA AUGCCUGGCG

30

(2) INFORMATION FOR SEQ ID NO:80:

(1) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 30 base pairs

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(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(X1) SEQUENCE DESCRIPTION: SEQ ID NO:80:
AGGUCACUCC GGCACCGUAC AGGCCUGGCC

30

(2) INFORMATION FOR SEQ ID NO:81:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(X1) SEQUENCE DESCRIPTION: SEQ ID NO:81:
GGACACUCC AACGAGGUA CGUACCGCC

30

(2) INFORMATION FOR SEQ ID NO:82:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(X1) SEQUENCE DESCRIPTION: SEQ ID NO:82:
GGGGCAAGC UACAGACAG UGCACCCAC

30

(2) INFORMATION FOR SEQ ID NO:83:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(X1) SEQUENCE DESCRIPTION: SEQ ID NO:83:
GGGGCAAGC UACAGACAG UGCACCCAC

30

(2) INFORMATION FOR SEQ ID NO:84:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(X1) SEQUENCE DESCRIPTION: SEQ ID NO:84:
GGGGCAAGC UACAGACAG UGCACCCAC

30

(2) INFORMATION FOR SEQ ID NO:85:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(X1) SEQUENCE DESCRIPTION: SEQ ID NO:85:
UGGGUGCUA CCAGACACA CCCAGCTGU

30

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(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(X1) SEQUENCE DESCRIPTION: SEQ ID NO:86:
CCGAGGUAU CGUUGGUCA AGCACCUC

30

(2) INFORMATION FOR SEQ ID NO:87:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(X1) SEQUENCE DESCRIPTION: SEQ ID NO:87:
GGGAAGCU AUCAGAGAU GCACCCGCA

30

(2) INFORMATION FOR SEQ ID NO:88:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(X1) SEQUENCE DESCRIPTION: SEQ ID NO:88:
GGGAAGCU AUCAGAGAU GCACCCGCA

30

(2) INFORMATION FOR SEQ ID NO:89:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(X1) SEQUENCE DESCRIPTION: SEQ ID NO:89:
ACUUCACUG CAUUCGAAU UCAUGCCTUG

30

(2) INFORMATION FOR SEQ ID NO:90:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(X1) SEQUENCE DESCRIPTION: SEQ ID NO:90:
GCAUGAAGC GAUUCUAGU ACGGACCA

30

(2) INFORMATION FOR SEQ ID NO:91:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(X1) SEQUENCE DESCRIPTION: SEQ ID NO:91:
GCAUGAAGC GAUUCUAGU ACGGACCA

30

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- (2) INFORMATION FOR SEQ ID NO:92:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) SEQUENCE DESCRIPTION: SEQ ID NO:92:
AGGUNAAGU ACUGCAAGC UCACUCGACG 30
- (2) INFORMATION FOR SEQ ID NO:93:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) SEQUENCE DESCRIPTION: SEQ ID NO:93:
AGGUNAAGU ACUGCAAGC UCACUCGACG 30
- (2) INFORMATION FOR SEQ ID NO:94:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) SEQUENCE DESCRIPTION: SEQ ID NO:94:
GGUAAAGCU UGACAAAGU CACCAAGTGC 30
- (2) INFORMATION FOR SEQ ID NO:95:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 76 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-NH₂ cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-NH₂ uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:95:
GGAGACAG AAUAGGCTC AANNNNNNN NNNNNNNNN 50
NNUCCAGAG GAGGUCACA ACAGGC 76
- (2) INFORMATION FOR SEQ ID NO:96:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 39 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) SEQUENCE DESCRIPTION: SEQ ID NO:96:
TAATACACT CACTATAGG AGACAGAAU AACGUCAA 39
- (2) INFORMATION FOR SEQ ID NO:97:
(1) SEQUENCE CHARACTERISTICS:

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- (2) INFORMATION FOR SEQ ID NO:98:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 24 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) SEQUENCE DESCRIPTION: SEQ ID NO:97:
GCCTTTGTG AGCTCTCTGT CGAA 24
- (2) INFORMATION FOR SEQ ID NO:99:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 81 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-NH₂ cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-NH₂ uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:98:
GGAGAGAGA UCGGNNNNN NNNNNNNNN NNNNNNNNN 50
NNNNNNNNN NNNNNCAGC GACTGCCCC A 81
- (2) INFORMATION FOR SEQ ID NO:99:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 32 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) SEQUENCE DESCRIPTION: SEQ ID NO:99:
TAATACACT CACTATAGG AGACGAUCC GG 32
- (2) INFORMATION FOR SEQ ID NO:100:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) SEQUENCE DESCRIPTION: SEQ ID NO:100:
TCGGGCGAGT CGCTG 16
- (2) INFORMATION FOR SEQ ID NO:101:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-NH₂ cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-NH₂ uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:101:
ACANGAGUU GUUGGAGG CAGGGGAGG 30

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- (2) INFORMATION FOR SEQ ID NO:102:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(1x) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-NH₂ cytosine
(1x) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-NH₂ uracil
(1x) SEQUENCE DESCRIPTION: SEQ ID NO:102:
UUGUGGAG GCAGUGGAG GUUCAGUGU 30
- (2) INFORMATION FOR SEQ ID NO:103:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(1x) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-NH₂ cytosine
(1x) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-NH₂ uracil
(1x) SEQUENCE DESCRIPTION: SEQ ID NO:103:
AAAGUGUG GGAAGACAG GGAAGUGAA 30
- (2) INFORMATION FOR SEQ ID NO:104:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(1x) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-NH₂ cytosine
(1x) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-NH₂ uracil
(1x) SEQUENCE DESCRIPTION: SEQ ID NO:104:
GUAGACUAAU GUGUGAAGA CAGCGGUGG 30
- (2) INFORMATION FOR SEQ ID NO:105:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(1x) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-NH₂ cytosine
(1x) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-NH₂ uracil
(1x) SEQUENCE DESCRIPTION: SEQ ID NO:105:
NNAUGUGUG GGAAGACAG GGGGGUGGA 30

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- (2) INFORMATION FOR SEQ ID NO:106:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(1x) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-NH₂ cytosine
(1x) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-NH₂ uracil
(1x) SEQUENCE DESCRIPTION: SEQ ID NO:106:
GGUGUGNCA KACAGUGGG UNGUGUAGC 30
- (2) INFORMATION FOR SEQ ID NO:107:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(1x) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-NH₂ cytosine
(1x) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-NH₂ uracil
(1x) SEQUENCE DESCRIPTION: SEQ ID NO:107:
AUGGUGUG GAAAGACAG GUGUGUCA 30
- (2) INFORMATION FOR SEQ ID NO:108:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(1x) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-NH₂ cytosine
(1x) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-NH₂ uracil
(1x) SEQUENCE DESCRIPTION: SEQ ID NO:108:
ACUGUGUGU GGAAGACAC GGGUGGUGA 30
- (2) INFORMATION FOR SEQ ID NO:109:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(1x) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-NH₂ cytosine
(1x) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-NH₂ uracil
(1x) SEQUENCE DESCRIPTION: SEQ ID NO:109:
AUAUGAGCU GUGUGUAGA CAGUGGUGG 30

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- (2) INFORMATION FOR SEQ ID NO:110:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(1x) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-NH₂ cytosine
(1x) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-NH₂ uracil
(1x) SEQUENCE DESCRIPTION: SEQ ID NO:110:
GAUGUGGGA GGGCAGUGGG GGGUACCAUA 30
- (2) INFORMATION FOR SEQ ID NO:111:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(1x) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-NH₂ cytosine
(1x) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-NH₂ uracil
(1x) SEQUENCE DESCRIPTION: SEQ ID NO:111:
GGGUGCAGG AACGUGGUG GUGUGUGU 30
- (2) INFORMATION FOR SEQ ID NO:112:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(1x) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-NH₂ cytosine
(1x) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-NH₂ uracil
(1x) SEQUENCE DESCRIPTION: SEQ ID NO:112:
UGUGUGGUG CGCAGUGUG GAAGCAGAG GAGGUGUAGA AUCAGUACGU 50
- (2) INFORMATION FOR SEQ ID NO:113:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(1x) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-NH₂ cytosine
(1x) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-NH₂ uracil
(1x) SEQUENCE DESCRIPTION: SEQ ID NO:113:
ACGACCGUG UGUGAAGAC AGUGGAGUG UUUUACGUA GUGAUGGCGC 50

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- (2) INFORMATION FOR SEQ ID NO:114:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 49 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(1x) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-NH₂ cytosine
(1x) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-NH₂ uracil
(1x) SEQUENCE DESCRIPTION: SEQ ID NO:114:
GGUGGCGGC GCAUGUGUG AAGACAGAG GAGGUGUAGA UCGUGCCG 49
- (2) INFORMATION FOR SEQ ID NO:115:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(1x) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-NH₂ cytosine
(1x) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-NH₂ uracil
(1x) SEQUENCE DESCRIPTION: SEQ ID NO:115:
GAAACUAGG GUGUGUGAA GACAGUGGA GUGUGCAGU CUUGGCCGU 50
- (2) INFORMATION FOR SEQ ID NO:116:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 49 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(1x) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-NH₂ cytosine
(1x) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-NH₂ uracil
(1x) SEQUENCE DESCRIPTION: SEQ ID NO:116:
UCCAGUGGG AAGACAGGG GAGGUGUAGA UCAUGAGCUC AAGACACUC 49
- (2) INFORMATION FOR SEQ ID NO:117:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(1x) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-NH₂ cytosine
(1x) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-NH₂ uracil
(1x) SEQUENCE DESCRIPTION: SEQ ID NO:117:
UGUAGUUUG GUGAAGACA GUGGAGGUG UGUAGUGAGA UUGGCGAGG 50

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- (2) INFORMATION FOR SEQ ID NO:118:
 (1) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 23 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear
 (ix) FEATURE:
 (D) OTHER INFORMATION: All C's are 2'-NH₂ cytosine
 (ix) FEATURE:
 (D) OTHER INFORMATION: All U's are 2'-NH₂ uracil
 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:118:
 UGUGUGAAG ACAGUGGAG GGU 23
- (2) INFORMATION FOR SEQ ID NO:119:
 (1) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 30 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear
 (ix) FEATURE:
 (D) OTHER INFORMATION: All C's are 2'-NH₂ cytosine
 (ix) FEATURE:
 (D) OTHER INFORMATION: All U's are 2'-NH₂ uracil
 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:119:
 UGUGUGAAG GUUACCUAG UGGGGAUGG 30
- (2) INFORMATION FOR SEQ ID NO:120:
 (1) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 31 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear
 (ix) FEATURE:
 (D) OTHER INFORMATION: All C's are 2'-NH₂ cytosine
 (ix) FEATURE:
 (D) OTHER INFORMATION: All U's are 2'-NH₂ uracil
 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:120:
 AAGACUGGU GGAAGGGUG UAGGGGUGG G 31
- (2) INFORMATION FOR SEQ ID NO:121:
 (1) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 49 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear
 (ix) FEATURE:
 (D) OTHER INFORMATION: All C's are 2'-NH₂ cytosine
 (ix) FEATURE:
 (D) OTHER INFORMATION: All U's are 2'-NH₂ uracil
 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:121:
 UAGGGCCGA ACUGUGGGA AGGAGGAGU GGUCAUGGG GUGGGGCTG 49

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- (2) INFORMATION FOR SEQ ID NO:122:
 (1) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 30 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear
 (ix) FEATURE:
 (D) OTHER INFORMATION: All C's are 2'-NH₂ cytosine
 (ix) FEATURE:
 (D) OTHER INFORMATION: All U's are 2'-NH₂ uracil
 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:122:
 UGUGUGAAG GANNUGAG UGGGUGUGG 30
- (2) INFORMATION FOR SEQ ID NO:123:
 (1) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 50 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear
 (ix) FEATURE:
 (D) OTHER INFORMATION: All C's are 2'-NH₂ cytosine
 (ix) FEATURE:
 (D) OTHER INFORMATION: All U's are 2'-NH₂ uracil
 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:123:
 AUUUGUGGG AUAGGCAUA GAGGUGUGG GAAACCCAG ACCGGGCGU 50
- (2) INFORMATION FOR SEQ ID NO:124:
 (1) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 51 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear
 (ix) FEATURE:
 (D) OTHER INFORMATION: All C's are 2'-NH₂ cytosine
 (ix) FEATURE:
 (D) OTHER INFORMATION: All U's are 2'-NH₂ uracil
 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:124:
 UGUGUGGAC AGCGGAGUC GGUUGUGGA GCGCAUACA UCCACUUGC U 51
- (2) INFORMATION FOR SEQ ID NO:125:
 (1) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 50 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear
 (ix) FEATURE:
 (D) OTHER INFORMATION: All C's are 2'-NH₂ cytosine
 (ix) FEATURE:
 (D) OTHER INFORMATION: All U's are 2'-NH₂ uracil
 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:125:
 AANNUNUGC AUGUGUGGA CAGGUGCAU GUGGUGUGG GACCUUGCU 50

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- (2) INFORMATION FOR SEQ ID NO:126:
- (1) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 31 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear
- (1X) FEATURE:
- (D) OTHER INFORMATION: All C's are 2'-NH₂ cytosine
- (1X) FEATURE:
- (D) OTHER INFORMATION: All U's are 2'-NH₂ uracil
- (1X) SEQUENCE DESCRIPTION: SEQ ID NO:126:
- UUGUGGAC AGGAGUANA NCGGUGGG A 31
- (2) INFORMATION FOR SEQ ID NO:127:
- (1) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 30 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear
- (1X) FEATURE:
- (D) OTHER INFORMATION: All C's are 2'-NH₂ cytosine
- (1X) FEATURE:
- (D) OTHER INFORMATION: All U's are 2'-NH₂ uracil
- (1X) SEQUENCE DESCRIPTION: SEQ ID NO:127:
- GCAGAGAU AGGAGUGGA UGGGUGGA 30
- (2) INFORMATION FOR SEQ ID NO:128:
- (1) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 30 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear
- (1X) FEATURE:
- (D) OTHER INFORMATION: All C's are 2'-NH₂ cytosine
- (1X) FEATURE:
- (D) OTHER INFORMATION: All U's are 2'-NH₂ uracil
- (1X) SEQUENCE DESCRIPTION: SEQ ID NO:128:
- UGAGAGUG AGGAGUGA GCGGAGGA 30
- (2) INFORMATION FOR SEQ ID NO:129:
- (1) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 30 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear
- (1X) FEATURE:
- (D) OTHER INFORMATION: All C's are 2'-NH₂ cytosine
- (1X) FEATURE:
- (D) OTHER INFORMATION: All U's are 2'-NH₂ uracil
- (1X) SEQUENCE DESCRIPTION: SEQ ID NO:129:
- GUGAUGGA AGGUGUG GAGGAGAC 30

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- (2) INFORMATION FOR SEQ ID NO:130:
- (1) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 50 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear
- (1X) FEATURE:
- (D) OTHER INFORMATION: All C's are 2'-NH₂ cytosine
- (1X) FEATURE:
- (D) OTHER INFORMATION: All U's are 2'-NH₂ uracil
- (1X) SEQUENCE DESCRIPTION: SEQ ID NO:130:
- UAGGAGUGA UGGGUGGA ACAGAGUUCU AADUGGAC UCACAGUGG 50
- (2) INFORMATION FOR SEQ ID NO:131:
- (1) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 50 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear
- (1X) FEATURE:
- (D) OTHER INFORMATION: All C's are 2'-NH₂ cytosine
- (1X) FEATURE:
- (D) OTHER INFORMATION: All U's are 2'-NH₂ uracil
- (1X) SEQUENCE DESCRIPTION: SEQ ID NO:131:
- CAGAGUGA UGGGUGGA ACAGAGUUCU AADUGGAC UCACAGUGG 50
- (2) INFORMATION FOR SEQ ID NO:132:
- (1) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 50 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear
- (1X) FEATURE:
- (D) OTHER INFORMATION: All C's are 2'-NH₂ cytosine
- (1X) FEATURE:
- (D) OTHER INFORMATION: All U's are 2'-NH₂ uracil
- (1X) SEQUENCE DESCRIPTION: SEQ ID NO:132:
- CAGAGUGA UGGGUGGA ACAGAGUUCU AADUGGAC UCACAGUGG 50
- (2) INFORMATION FOR SEQ ID NO:133:
- (1) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 14 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear
- (1X) FEATURE:
- (D) OTHER INFORMATION: All C's are 2'-NH₂ cytosine
- (1X) FEATURE:
- (D) OTHER INFORMATION: All U's are 2'-NH₂ uracil
- (1X) SEQUENCE DESCRIPTION: SEQ ID NO:133:
- GGAUGGAG GGGU 14

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- (2) INFORMATION FOR SEQ ID NO:134:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(1x) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-NH₂ cytosine
(1x) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-NH₂ uracil
(1x) SEQUENCE DESCRIPTION: SEQ ID NO:134:
UUAAGCGCGU GGUCCAGAGG UGGCGAGUAC 30
- (2) INFORMATION FOR SEQ ID NO:135:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(1x) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-NH₂ cytosine
(1x) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-NH₂ uracil
(1x) SEQUENCE DESCRIPTION: SEQ ID NO:135:
GACUAGGGCC GGACCGGCGG UGGUGAGUGG 30
- (2) INFORMATION FOR SEQ ID NO:136:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 47 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(1x) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-NH₂ cytosine
(1x) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-NH₂ uracil
(1x) SEQUENCE DESCRIPTION: SEQ ID NO:136:
AGUGGACGUG GCGGUGGAG GUGAGUGGUG AGACUGGUGU UGGGCGCU 47
- (2) INFORMATION FOR SEQ ID NO:137:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 49 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(1x) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-NH₂ cytosine
(1x) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-NH₂ uracil
(1x) SEQUENCE DESCRIPTION: SEQ ID NO:137:
CGUGGUCG UGGUGUGUGA GAUGAGACU AUAUGGUGG UAGACCGCU 49

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- (2) INFORMATION FOR SEQ ID NO:138:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(1x) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-NH₂ cytosine
(1x) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-NH₂ uracil
(1x) SEQUENCE DESCRIPTION: SEQ ID NO:138:
CCGUGGUGG UGAGU 15
- (2) INFORMATION FOR SEQ ID NO:139:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(1x) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-NH₂ cytosine
(1x) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-NH₂ uracil
(1x) SEQUENCE DESCRIPTION: SEQ ID NO:139:
MAAUAACAG AGAGAGACAU AUAUGACTCA ACAUAUAUUG AUUACAGAU 50
- (2) INFORMATION FOR SEQ ID NO:140:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 51 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(1x) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-NH₂ cytosine
(1x) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-NH₂ uracil
(1x) SEQUENCE DESCRIPTION: SEQ ID NO:140:
GAGUAACAG AAGAGACCU AGUGAGUCA ACAUAUAUUG AUUACAGAU 50
- (2) INFORMATION FOR SEQ ID NO:141:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(1x) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-NH₂ cytosine
(1x) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-NH₂ uracil
(1x) SEQUENCE DESCRIPTION: SEQ ID NO:141:
AGGUGGCGG GAAGAACCGG CGGUGAUGG GUGACAGAU GAUGUUCGU 50

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- (2) INFORMATION FOR SEQ ID NO:142:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-NH₂, cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-NH₂, uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:142:
GAGGUGGCA GGGAGGACC GCGUGAUC GUGACACAG UAGUUGCGU 50
- (2) INFORMATION FOR SEQ ID NO:143:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-NH₂, cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-NH₂, uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:143:
CGGAGGCGU GCGGGGUG GUGGGUGA 30
- (2) INFORMATION FOR SEQ ID NO:144:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-NH₂, cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-NH₂, uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:144:
CGGAGGCGU ACGAGCGUG GGGGGUGA AACAGGUGU GCUUGGCGG 50
- (2) INFORMATION FOR SEQ ID NO:145:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-NH₂, cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-NH₂, uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:145:
GAUUGGAAG AGGUGUGG UAGGAGGCG 30

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- (2) INFORMATION FOR SEQ ID NO:146:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-NH₂, cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-NH₂, uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:146:
GACCAAGU UAAAGCCCA UCAAGGUG GGUUGGGU ACGAGGCGU 50
- (2) INFORMATION FOR SEQ ID NO:147:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-NH₂, cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-NH₂, uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:147:
CGGAGGCGU GCGGGGUG GUGGGUGA 30
- (2) INFORMATION FOR SEQ ID NO:148:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-NH₂, cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-NH₂, uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:148:
UGGCGCGCG GUCUGGUG UAUUGUGA 30
- (2) INFORMATION FOR SEQ ID NO:149:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-NH₂, cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-NH₂, uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:149:
AGUGGGGCG UCGUGGCG UGGGCGGCG 30

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- (2) INFORMATION FOR SEQ ID NO:150:
 (1) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 30 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear
 (ix) FEATURE:
 (D) OTHER INFORMATION: All C's are 2'-NH₂ cytosine
 (ix) FEATURE:
 (D) OTHER INFORMATION: All U's are 2'-NH₂ uracil
 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:150:
 GGAGUGUG GAGACCGGGA GAUGGAGGA 30
- (2) INFORMATION FOR SEQ ID NO:151:
 (1) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 30 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear
 (ix) FEATURE:
 (D) OTHER INFORMATION: All C's are 2'-NH₂ cytosine
 (ix) FEATURE:
 (D) OTHER INFORMATION: All U's are 2'-NH₂ uracil
 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:151:
 AAGCGGCG AUGGAAAGUG UGGGUAAGA 30
- (2) INFORMATION FOR SEQ ID NO:152:
 (1) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 30 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear
 (ix) FEATURE:
 (D) OTHER INFORMATION: All C's are 2'-NH₂ cytosine
 (ix) FEATURE:
 (D) OTHER INFORMATION: All U's are 2'-NH₂ uracil
 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:152:
 GAGAGGAGUG GAGAGAGCG GUGUGCAGGG 30
- (2) INFORMATION FOR SEQ ID NO:153:
 (1) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 30 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear
 (ix) FEATURE:
 (D) OTHER INFORMATION: All C's are 2'-NH₂ cytosine
 (ix) FEATURE:
 (D) OTHER INFORMATION: All U's are 2'-NH₂ uracil
 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:153:
 GAGAGGUGA AUGGGGACG AUGGGGUGG 30

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- (2) INFORMATION FOR SEQ ID NO:154:
 (1) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 49 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear
 (ix) FEATURE:
 (D) OTHER INFORMATION: All C's are 2'-NH₂ cytosine
 (ix) FEATURE:
 (D) OTHER INFORMATION: All U's are 2'-NH₂ uracil
 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:154:
 CUGAAAUUGC GGGUGUGAG GUUUGUGUG AAGUGUGAU GGUACAGU 49
- (2) INFORMATION FOR SEQ ID NO:155:
 (1) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 50 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear
 (ix) FEATURE:
 (D) OTHER INFORMATION: All C's are 2'-NH₂ cytosine
 (ix) FEATURE:
 (D) OTHER INFORMATION: All U's are 2'-NH₂ uracil
 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:155:
 CAUGUGUGG AGUCUGCUA UGUGGUGGG UGACGCUAC CGAUGUUC 50
- (2) INFORMATION FOR SEQ ID NO:156:
 (1) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 48 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear
 (ix) FEATURE:
 (D) OTHER INFORMATION: All C's are 2'-NH₂ cytosine
 (ix) FEATURE:
 (D) OTHER INFORMATION: All U's are 2'-NH₂ uracil
 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:156:
 ACGGGGAGU ACGAGAGCG ACTGUAGUC UAGUGGUCU GUUGGUG 48
- (2) INFORMATION FOR SEQ ID NO:157:
 (1) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 50 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear
 (ix) FEATURE:
 (D) OTHER INFORMATION: All C's are 2'-NH₂ cytosine
 (ix) FEATURE:
 (D) OTHER INFORMATION: All U's are 2'-NH₂ uracil
 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:157:
 UUCAGCGGCG AUUAGUGCAG CGGUCUAC AAAGAGGUG UUGUGUGUC 50

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- (2) INFORMATION FOR SEQ ID NO:158:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-NH₂ cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-NH₂ uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:158:
CGAGTGGGUU GGUGGGGAG GGAGAGUUU ACACUACCC GUGGUGGCU 50
- (2) INFORMATION FOR SEQ ID NO:159:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-NH₂ cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-NH₂ uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:159:
GGUGUGUAC AAGUGGGUG GGUGGGGAG GUACAAAGC UUGGGGUGU 50
- (2) INFORMATION FOR SEQ ID NO:160:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-NH₂ cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-NH₂ uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:160:
AAGCGAGGU ACAGAGCGG GAGCGAUAU AAGAGAAAU CUGGACAGU 50
- (2) INFORMATION FOR SEQ ID NO:161:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-NH₂ cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-NH₂ uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:161:
AGCGAUAUU GGGGUGGUC AGCCGCUCC CAAGACUCC ACCUAGCCC 50

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- (2) INFORMATION FOR SEQ ID NO:162:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-NH₂ cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-NH₂ uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:162:
GGGUGGGUG GCAAGCGAG ACAGAGGUU GGUGGGAU CAUUGGUGU 50
- (2) INFORMATION FOR SEQ ID NO:163:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-NH₂ cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-NH₂ uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:163:
GGAGGGGAG GUUGAUGCG GAGCGACUG ACCAGAGAA AUGUGCGGU 50
- (2) INFORMATION FOR SEQ ID NO:164:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-NH₂ cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-NH₂ uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:164:
CUAGCAUCC AGAAGAGGA CUUGUAGGG CACCAUCAG AUUUUGGCU 50
- (2) INFORMATION FOR SEQ ID NO:165:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-NH₂ cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-NH₂ uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:165:
ACCUAGGCA UCCAGUGUG GGAUAGCGU UGAGAGAAU GUGUUGGUC 50

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- (2) INFORMATION FOR SEQ ID NO:166:
- (1) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 30 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear
 - (1x) FEATURE:
 - (D) OTHER INFORMATION: All C's are 2'-NH₂ cytosine
 - (1x) FEATURE:
 - (D) OTHER INFORMATION: All U's are 2'-NH₂ uracil
 - (x1) SEQUENCE DESCRIPTION: SEQ ID NO:166:
 CAGGAGAG GAGGUCAGAC UAGCGGUA
 30
- (2) INFORMATION FOR SEQ ID NO:167:
- (1) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 30 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear
 - (1x) FEATURE:
 - (D) OTHER INFORMATION: All C's are 2'-NH₂ cytosine
 - (1x) FEATURE:
 - (D) OTHER INFORMATION: All U's are 2'-NH₂ uracil
 - (x1) SEQUENCE DESCRIPTION: SEQ ID NO:167:
 UACGGGGAA GAGGGAUUG GCAAGAGCA
 30
- (2) INFORMATION FOR SEQ ID NO:168:
- (1) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 30 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear
 - (1x) FEATURE:
 - (D) OTHER INFORMATION: All C's are 2'-NH₂ cytosine
 - (1x) FEATURE:
 - (D) OTHER INFORMATION: All U's are 2'-NH₂ uracil
 - (x1) SEQUENCE DESCRIPTION: SEQ ID NO:168:
 AAAAGUUGU GGAAGACAU GGGAGUGAA
 30
- (2) INFORMATION FOR SEQ ID NO:169:
- (1) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 30 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear
 - (1x) FEATURE:
 - (D) OTHER INFORMATION: All C's are 2'-NH₂ cytosine
 - (1x) FEATURE:
 - (D) OTHER INFORMATION: All U's are 2'-NH₂ uracil
 - (x1) SEQUENCE DESCRIPTION: SEQ ID NO:169:
 UGAGGCGGU AGUGAGGUA AUGGCGUNA
 30

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- (2) INFORMATION FOR SEQ ID NO:170:
- (1) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 30 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear
 - (1x) FEATURE:
 - (D) OTHER INFORMATION: All C's are 2'-NH₂ cytosine
 - (1x) FEATURE:
 - (D) OTHER INFORMATION: All U's are 2'-NH₂ uracil
 - (x1) SEQUENCE DESCRIPTION: SEQ ID NO:170:
 UAGGAGUG GAGGAAGCU UCACAGCGA
 30
- (2) INFORMATION FOR SEQ ID NO:171:
- (1) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 30 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear
 - (1x) FEATURE:
 - (D) OTHER INFORMATION: All C's are 2'-NH₂ cytosine
 - (1x) FEATURE:
 - (D) OTHER INFORMATION: All U's are 2'-NH₂ uracil
 - (x1) SEQUENCE DESCRIPTION: SEQ ID NO:171:
 UGAGGAGAG GAGGACAGCA UGCACAGAU
 30
- (2) INFORMATION FOR SEQ ID NO:172:
- (1) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 30 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear
 - (1x) FEATURE:
 - (D) OTHER INFORMATION: All C's are 2'-NH₂ cytosine
 - (1x) FEATURE:
 - (D) OTHER INFORMATION: All U's are 2'-NH₂ uracil
 - (x1) SEQUENCE DESCRIPTION: SEQ ID NO:172:
 GUAGAGAGG UGAGAGUUG AGUGUGCAA
 30
- (2) INFORMATION FOR SEQ ID NO:173:
- (1) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 30 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear
 - (1x) FEATURE:
 - (D) OTHER INFORMATION: All C's are 2'-NH₂ cytosine
 - (1x) FEATURE:
 - (D) OTHER INFORMATION: All U's are 2'-NH₂ uracil
 - (x1) SEQUENCE DESCRIPTION: SEQ ID NO:173:
 CGUCAGGUC GAUGGAGAG GAGGAGUCA
 30

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- (2) INFORMATION FOR SEQ ID NO:174:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-NH₂ cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-NH₂ uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:174:
GGGGUCAGG ACAGGGGUG GUGGGGUGU 30
- (2) INFORMATION FOR SEQ ID NO:175:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-NH₂ cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-NH₂ uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:175:
GGAGGAGGA GGAUGAUGA GUCACACAG 30
- (2) INFORMATION FOR SEQ ID NO:176:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-NH₂ cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-NH₂ uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:176:
CAACGAGG GGAUGGAG GAG 23
- (2) INFORMATION FOR SEQ ID NO:177:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-NH₂ cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-NH₂ uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:177:
AGGGGUGUC GUUAGCUCG GUGGGUGUG 30

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- (2) INFORMATION FOR SEQ ID NO:178:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 31 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-NH₂ cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-NH₂ uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:178:
AGGAGGUA AGAGGAGGA UUAAGCUG G 31
- (2) INFORMATION FOR SEQ ID NO:179:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-NH₂ cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-NH₂ uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:179:
GUGAGGUA GUGAGGAGG AGAGGACA 29
- (2) INFORMATION FOR SEQ ID NO:180:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-NH₂ cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-NH₂ uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:180:
AUAUUCAG GAGGUGAGG ACAGUGCGC 30
- (2) INFORMATION FOR SEQ ID NO:181:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-NH₂ cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-NH₂ uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:181:
GAUGAGGACU CGGGCGGAG GUGGUAACA 30

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- (2) INFORMATION FOR SEQ ID NO:182:
- (1) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 50 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear
- (1x) FEATURE:
- (D) OTHER INFORMATION: All C's are 2'-NH₂ cytosine
- (1x) FEATURE:
- (D) OTHER INFORMATION: All U's are 2'-NH₂ uracil
- (1x1) SEQUENCE DESCRIPTION: SEQ ID NO:182:
- AGGUGGCGC UGGGAUUCG CUUGACAGG CUUGGUGG 50
- (2) INFORMATION FOR SEQ ID NO:183:
- (1) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 43 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear
- (1x) FEATURE:
- (D) OTHER INFORMATION: All C's are 2'-NH₂ cytosine
- (1x) FEATURE:
- (D) OTHER INFORMATION: All U's are 2'-NH₂ uracil
- (1x1) SEQUENCE DESCRIPTION: SEQ ID NO:183:
- AAAGUAGUCA UCGGCAAC UCGGAGUCA CUGCUGGGA UCC 43
- (2) INFORMATION FOR SEQ ID NO:184:
- (1) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 50 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear
- (1x) FEATURE:
- (D) OTHER INFORMATION: All C's are 2'-NH₂ cytosine
- (1x) FEATURE:
- (D) OTHER INFORMATION: All U's are 2'-NH₂ uracil
- (1x1) SEQUENCE DESCRIPTION: SEQ ID NO:184:
- GACCAAGAU UAAACGCCA UCAAGGUGG GGGUGGGGA AGAGGCGUG 50
- (2) INFORMATION FOR SEQ ID NO:185:
- (1) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 50 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear
- (1x) FEATURE:
- (D) OTHER INFORMATION: All C's are 2'-NH₂ cytosine
- (1x) FEATURE:
- (D) OTHER INFORMATION: All U's are 2'-NH₂ uracil
- (1x1) SEQUENCE DESCRIPTION: SEQ ID NO:185:
- CGCGAGUCU ACAGGCGUG GGGGGUGGA AACUAGUUGU GCUUGGCGC 50

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- (2) INFORMATION FOR SEQ ID NO:186:
- (1) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 26 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear
- (1x1) SEQUENCE DESCRIPTION: SEQ ID NO:186:
- GGUGUGGA AGACGCGG UGGUUC 26
- (2) INFORMATION FOR SEQ ID NO:187:
- (1) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 27 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear
- (1x1) SEQUENCE DESCRIPTION: SEQ ID NO:187:
- GGACGGGUG GUGGAGGUG GCGGAGU 27
- (2) INFORMATION FOR SEQ ID NO:188:
- (1) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 38 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear
- (1x1) SEQUENCE DESCRIPTION: SEQ ID NO:188:
- GGAGGAGAU GCGGACGGG AGGUACAGA GCGGAGC 38
- (2) INFORMATION FOR SEQ ID NO:189:
- (1) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 15 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear
- (1x1) SEQUENCE DESCRIPTION: SEQ ID NO:189:
- GATTGGTGG GTTGG 15
- (2) INFORMATION FOR SEQ ID NO:190:
- (1) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 18 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear
- (1x1) SEQUENCE DESCRIPTION: SEQ ID NO:190:
- GAUCGAAAG NAUAGGC 18
- (2) INFORMATION FOR SEQ ID NO:191:
- (1) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 21 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear
- (1x1) SEQUENCE DESCRIPTION: SEQ ID NO:191:

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GGGCGTUGG GCGCGGUGU U

21

(2) INFORMATION FOR SEQ ID NO:192:

(1) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 76 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(x1) SEQUENCE DESCRIPTION: SEQ ID NO:192:

AGAGCCUGU CGAGCAUGU GAGAGUGAA GUAGAGAGC UUGGUGUGU
CGAGCUAAA CAGCUUUGC GACGG 76

50

(2) INFORMATION FOR SEQ ID NO:193:

(1) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 74 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(x1) SEQUENCE DESCRIPTION: SEQ ID NO:193:

AGAGCCUGU CGAGCAUGU GUAGUGAAG GAGAGUGAA GCGAGUCAG
UGAGCUAAA GCUUGUGCA CGGG 74

50

(2) INFORMATION FOR SEQ ID NO:194:

(1) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 75 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(x1) SEQUENCE DESCRIPTION: SEQ ID NO:194:

AGAGCCUGU CGAGCAUGU GAUAGACAG AUGAGAGAA GUAGCGUGG
GUGAGCUAAC AGCUUUGC AGCG 75

50

(2) INFORMATION FOR SEQ ID NO:195:

(1) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 76 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(x1) SEQUENCE DESCRIPTION: SEQ ID NO:195:

AGAGCCUGU CGAGCAUGU GCUUUGCCG GUUGCAAGU CAGUAGGCCG
CGAGCUAAA CAGCUUUGC GACGG 76

50

(2) INFORMATION FOR SEQ ID NO:196:

(1) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 75 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(x1) SEQUENCE DESCRIPTION: SEQ ID NO:196:

AGAGCCUGU CGAGCAUGU GACCCGAGU CAGAGUAGU AGGCGGAGU
GUAGCUAAC AGCUUUGC AGCG 75

50

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(2) INFORMATION FOR SEQ ID NO:197:

(1) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 76 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(x1) SEQUENCE DESCRIPTION: SEQ ID NO:197:

AGAGCCUGU CGAGCAUGU GUAGAGAGU CAGAGUAGU AGGCGAGU
CGAGCUAAA CAGCUUUGC GACGG 76

50

(2) INFORMATION FOR SEQ ID NO:198:

(1) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 76 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(x1) SEQUENCE DESCRIPTION: SEQ ID NO:198:

AGAGCCUGU CGAGCAUGU GCAGCGAGU CAGAGUAGU AGGCGAGU
CGAGCUAAA CAGCUUUGC GACGG 76

50

(2) INFORMATION FOR SEQ ID NO:199:

(1) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 76 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(x1) SEQUENCE DESCRIPTION: SEQ ID NO:199:

AGAGCCUGU CGAGCAUGU GAUAGACAG GAUAGAGAG AGAGCCUGU
AGAGCUAAA CAGCUUUGC GACGG 76

50

(2) INFORMATION FOR SEQ ID NO:200:

(1) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 76 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(x1) SEQUENCE DESCRIPTION: SEQ ID NO:200:

AGAGCCUGU CGAGCAUGU GUAGAGAGU UGAGAGAGU UAGGCGAGU
CGAGCUAAA CAGCUUUGC GACGG 76

50

(2) INFORMATION FOR SEQ ID NO:201:

(1) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 69 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(x1) SEQUENCE DESCRIPTION: SEQ ID NO:201:

AGAGCCUGU CGAGCAUGU GAUAGAGAGU AGAGAGAGU UUGGUGAGU
AAACAGUUU GUACAGCG 75

50

(2) INFORMATION FOR SEQ ID NO:202:

(1) SEQUENCE CHARACTERISTICS:

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(A) LENGTH: 81 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(x1) SEQUENCE DESCRIPTION: SEQ ID NO:202:
AGAGCCUUCU CGAGCAUCGU GAGCGUGAG UCGAUCGAA AGUAGAGUAG
GCAUCUGAG CUAACAGCU UUGUCAGCG G

50
81

(2) INFORMATION FOR SEQ ID NO:203:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 75 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(x1) SEQUENCE DESCRIPTION: SEQ ID NO:203:
AGAGCCUUCU CGAGCAUCGU GAGCGUGAGU CAAAGGUAA GUAGCGCACT
GAGCUAAAC AGCUUUGUG ACAGG

50
75

(2) INFORMATION FOR SEQ ID NO:204:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 74 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(x1) SEQUENCE DESCRIPTION: SEQ ID NO:204:
AGAGCCUUCU CGAGCAUCGU GAUACACAG AUCGAAAGAG AGUAGCGCUG
UAGCUAAACA GCUUUGUGA CAGG

50
74

(2) INFORMATION FOR SEQ ID NO:205:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 76 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(x1) SEQUENCE DESCRIPTION: SEQ ID NO:205:
AGAGCCUUCU CGAGCAUCGU GUGUACTUGA UCGAAGUGAG UAGCGACGCA
CGUACGUAA CAGCUUUGUC GACGCG

50
76

(2) INFORMATION FOR SEQ ID NO:206:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 75 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(x1) SEQUENCE DESCRIPTION: SEQ ID NO:206:
AGAGCCUUCU CGAGCAUCGU GAUACACAG AUCGAAAGGAA AGUAGCGCUG
GUAGCUAAAC AGCUUUGUG ACAGG

50
75

(2) INFORMATION FOR SEQ ID NO:207:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 72 base pairs
(B) TYPE: nucleic acid

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(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(x1) SEQUENCE DESCRIPTION: SEQ ID NO:207:
AGAGCCUUCU CGAGCAUCGU GUGCGCGCUCU UGAGCGCCGU GCUUGAGCUA
GCUAAACAGC UUGUCAGCG G

50
72

(2) INFORMATION FOR SEQ ID NO:208:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 71 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(x1) SEQUENCE DESCRIPTION: SEQ ID NO:208:
AGAGCCUUCU CGAGCAUCGU GUGCGCGCUCU UGAGCGCCGU GCUUACGUAG
CUAAACAGCU UUGUCAGCG G

50
71

(2) INFORMATION FOR SEQ ID NO:209:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 72 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(x1) SEQUENCE DESCRIPTION: SEQ ID NO:209:
AGAGCCUUCU CGAGCAUCGU GUGCGCGCUCU UGAGCGCCGU GCUUACGU
GCUAAACAGC UUGUCAGCG G

50
72

(2) INFORMATION FOR SEQ ID NO:210:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 72 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(x1) SEQUENCE DESCRIPTION: SEQ ID NO:210:
AGAGCCUUCU CGAGCAUCGU GUGCGCGCUCU UGAGCGCCGU GCUUACGU
GCUAAACAGC UUGUCAGCG G

50
72

(2) INFORMATION FOR SEQ ID NO:211:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 79 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(x1) SEQUENCE DESCRIPTION: SEQ ID NO:211:
GGAGAGGCC UGAGCAGCAU GCUAGAGAC GAAGUAGUA GCGUUGUGCU
GCUUGAGCU AAACAGCUU GUGACGCG

50
79

(2) INFORMATION FOR SEQ ID NO:212:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 79 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

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(x1) SEQUENCE DESCRIPTION: SEQ ID NO:212:
GGGAGUCC UGUCAGCAU GCUCAUCG GAUCAGAU AGUAGCCGA
GUGGAGCU AAACAGCUU GUCAAGG 50

(2) INFORMATION FOR SEQ ID NO:213:
(1) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 79 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(x1) SEQUENCE DESCRIPTION: SEQ ID NO:213:
GGGAGUCC UGUCAGCAU GCUCAUCG GCGAGUACA GUGAGUAGC
GUGAGAGCU AAACAGCUU GUCAAGG 79

(2) INFORMATION FOR SEQ ID NO:214:

- (1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 75 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(x1) SEQUENCE DESCRIPTION: SEQ ID NO:214:
GGGAGUCC UGUCAGCAU GCUCAUCG CUUGAGCGC CGUCUUGAC
GUGAGUAGC AGCUUUGCG ACGGG 75

(2) INFORMATION FOR SEQ ID NO:215:

- (1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 75 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(x1) SEQUENCE DESCRIPTION: SEQ ID NO:215:
AGATCCCTGT CGAGCATCT NNNNNNNNN NNNNNNNNN NNNNNNNNN
GTAGCTAAC TCCTTGTG ACGGG 75

(2) INFORMATION FOR SEQ ID NO:216:

- (1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(x1) SEQUENCE DESCRIPTION: SEQ ID NO:216:
TCACTAGCT AGGTGTCAT GATCTAGT 30

(2) INFORMATION FOR SEQ ID NO:217:

- (1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(x1) SEQUENCE DESCRIPTION: SEQ ID NO:217:
GTCACTACC GTGTAGGA AGTGTGAGT 30

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(2) INFORMATION FOR SEQ ID NO:218:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(x1) SEQUENCE DESCRIPTION: SEQ ID NO:218:
ACTAGGGGG TAGTGTCGG TTGGGGTCTA 30

(2) INFORMATION FOR SEQ ID NO:219:

- (1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(x1) SEQUENCE DESCRIPTION: SEQ ID NO:219:
ACACCGTGG TAGGTAGA TGGGTGTC 30

(2) INFORMATION FOR SEQ ID NO:220:

- (1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(x1) SEQUENCE DESCRIPTION: SEQ ID NO:220:
GCACTTGTG TCCTGTAG GTAGATGCG 30

(2) INFORMATION FOR SEQ ID NO:221:

- (1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(x1) SEQUENCE DESCRIPTION: SEQ ID NO:221:
GTGATAGT AGGTGCGAT GGGCTACGT 30

(2) INFORMATION FOR SEQ ID NO:222:

- (1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(x1) SEQUENCE DESCRIPTION: SEQ ID NO:222:
GAGTTAGGG TAGGCGTAG ATGTGCAAC 30

(2) INFORMATION FOR SEQ ID NO:223:

- (1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(x1) SEQUENCE DESCRIPTION: SEQ ID NO:223:

W05071853

PCTUS9501458

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ATGCTACAC GTGCTAGGGA AGATGCTGT

30

(2) INFORMATION FOR SEQ ID NO:224:

(1) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 30 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(X1) SEQUENCE DESCRIPTION: SEQ ID NO:224:

30

GTGCTAGGGA GTTACGGAT GTTACGGAT

(2) INFORMATION FOR SEQ ID NO:225:

(1) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 30 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(X1) SEQUENCE DESCRIPTION: SEQ ID NO:225:

30

GTGCTAGGGA GTTACGGAT GTTACGGAT

(2) INFORMATION FOR SEQ ID NO:226:

(1) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 30 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(X1) SEQUENCE DESCRIPTION: SEQ ID NO:226:

30

GTGCTAGGGA GTTACGGAT GTTACGGAT

(2) INFORMATION FOR SEQ ID NO:227:

(1) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 30 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(X1) SEQUENCE DESCRIPTION: SEQ ID NO:227:

30

GTGCTAGGGA GTTACGGAT GTTACGGAT

(2) INFORMATION FOR SEQ ID NO:228:

(1) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 30 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(X1) SEQUENCE DESCRIPTION: SEQ ID NO:228:

30

GTGCTAGGGA GTTACGGAT GTTACGGAT

W05071853

PCTUS9501458

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ACGACCGCG CGACGACGAC TGAAGGCGC

30

(2) INFORMATION FOR SEQ ID NO:229:

(1) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 30 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(X1) SEQUENCE DESCRIPTION: SEQ ID NO:229:

30

ACGACCGCG CGACGACGAC TGAAGGCGC

(2) INFORMATION FOR SEQ ID NO:230:

(1) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 30 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(X1) SEQUENCE DESCRIPTION: SEQ ID NO:230:

30

ACGACCGCG CGACGACGAC TGAAGGCGC

(2) INFORMATION FOR SEQ ID NO:231:

(1) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 30 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(X1) SEQUENCE DESCRIPTION: SEQ ID NO:231:

30

ACGACCGCG CGACGACGAC TGAAGGCGC

(2) INFORMATION FOR SEQ ID NO:232:

(1) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 30 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(X1) SEQUENCE DESCRIPTION: SEQ ID NO:232:

30

ACGACCGCG CGACGACGAC TGAAGGCGC

(2) INFORMATION FOR SEQ ID NO:233:

(1) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 30 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(X1) SEQUENCE DESCRIPTION: SEQ ID NO:233:

30

ACGACCGCG CGACGACGAC TGAAGGCGC

(2) INFORMATION FOR SEQ ID NO:234:

(1) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 30 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(X1) SEQUENCE DESCRIPTION: SEQ ID NO:234:

30

ACGACCGCG CGACGACGAC TGAAGGCGC

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(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(x1) SEQUENCE DESCRIPTION: SEQ ID NO:235:
CGATCGCTGG TAGGGTAGGGT TAGGTGTCAAT

30

(2) INFORMATION FOR SEQ ID NO:236:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(x1) SEQUENCE DESCRIPTION: SEQ ID NO:236:
GGTATGCGGT AGGTGTGAGT GGAGCTACTT

30

(2) INFORMATION FOR SEQ ID NO:237:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(x1) SEQUENCE DESCRIPTION: SEQ ID NO:237:
GGCTTAACTT CCGGGTAGTG GTGGCTTGA

30

(2) INFORMATION FOR SEQ ID NO:238:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(x1) SEQUENCE DESCRIPTION: SEQ ID NO:238:
GGAGAGCGTA GGAGTAGAGT TGGAGCCGTA

30

(2) INFORMATION FOR SEQ ID NO:239:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(x1) SEQUENCE DESCRIPTION: SEQ ID NO:239:
GTGAATAGGT AGGCTCGAT AGGCTACGCT

30

(2) INFORMATION FOR SEQ ID NO:240:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 105 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(x1) SEQUENCE DESCRIPTION: SEQ ID NO:240:
AGATGCTGT CGAGCATGCT NNNNNNNNN NNNNNNNNN NNNNNNNNN
NNNNNNNNNN NNNNNNNNN NNNNNNNNN GTAGCTAAAC TGCTTTGTG
ACGGG

50
100
105

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(2) INFORMATION FOR SEQ ID NO:241:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 60 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(x1) SEQUENCE DESCRIPTION: SEQ ID NO:241:
GGAAGCCCGG GGAAGTCCCA GTGTAGGCT GAGGTTGGG GGAATTGAAT
CCGTGTGAC

50
60

(2) INFORMATION FOR SEQ ID NO:242:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 60 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(x1) SEQUENCE DESCRIPTION: SEQ ID NO:242:
GACGGGCGAG GAGGTGGCA GCAGGATGG GTTAGTGTA GCGCTGCA
CTCAGGATTG

50
60

(2) INFORMATION FOR SEQ ID NO:243:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 58 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(x1) SEQUENCE DESCRIPTION: SEQ ID NO:243:
AGCTGTGTC GTGCCGCTG GTGAGGTTG ATGCGTGGT AGGCTAGTCC
CATGGCGA

50
58

(2) INFORMATION FOR SEQ ID NO:244:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 60 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(x1) SEQUENCE DESCRIPTION: SEQ ID NO:244:
CTGCGAGTGG GACGAGCGT GTTAGGCGG GTTAGGTG TAGTCTCAGC
GGCTGGGCA

50
60

(2) INFORMATION FOR SEQ ID NO:245:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 60 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(x1) SEQUENCE DESCRIPTION: SEQ ID NO:245:
TGTGCTGAC TGCTAGTGA AGGTATGCC GGGGTATGG TGAGTTGGGG
TGCAATGAC

50
60

(2) INFORMATION FOR SEQ ID NO:246:
(1) SEQUENCE CHARACTERISTICS:

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(A) LENGTH: 60 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(x1) SEQUENCE DESCRIPTION: SEQ ID NO:246:
GCGCGCGTGG GTAGAGTGGC GCACGTGTGT TGGGCGGAGA GGCTAGGAGT
GCATGATGCC 50
60

(2) INFORMATION FOR SEQ ID NO:247:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 59 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(x1) SEQUENCE DESCRIPTION: SEQ ID NO:247:
AAGCCTGGA GCGGTTGGT TGGCGGGGT AGCCTAGGTG TGCAATGATGC
TACCCGAC 50
59

(2) INFORMATION FOR SEQ ID NO:248:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 60 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(x1) SEQUENCE DESCRIPTION: SEQ ID NO:248:
CCGTGATCA ACCGTCCAC GCTGCTTGC TGTGTAGGG GAGCATGAGC
CCAGAGTGG 50
60

(2) INFORMATION FOR SEQ ID NO:249:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 60 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(x1) SEQUENCE DESCRIPTION: SEQ ID NO:249:
AGCGATGTT GCGGTGATA CTCGATTGG TAGGCGAGGT TGGGCTCGGA
TAGCTCGGA 50
60

(2) INFORMATION FOR SEQ ID NO:250:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 60 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(x1) SEQUENCE DESCRIPTION: SEQ ID NO:250:
TGAGCAGGTG GTAGGGTTAG GGTGGGTGC CTGAGGCGTC CTGATCAGGC
GCGGGTAGG 50
60

(2) INFORMATION FOR SEQ ID NO:251:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 60 base pairs
(B) TYPE: nucleic acid

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(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(x1) SEQUENCE DESCRIPTION: SEQ ID NO:251:
GGAGTGGT CTTCGGGA GGTGTGTT GCGAGAGGG TAGGTCTGGA
TATCCCGGA 50
60

(2) INFORMATION FOR SEQ ID NO:252:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 60 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(x1) SEQUENCE DESCRIPTION: SEQ ID NO:252:
CTAGGCGCTG GTAGGGAGG TTGGAGTGG TACCTCCGC TGGCGGTGAT
TGTGCGAGG 50
60

(2) INFORMATION FOR SEQ ID NO:253:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 60 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(x1) SEQUENCE DESCRIPTION: SEQ ID NO:253:
CTGGGGGTGG GAGGAGGCT GTTAGGGAG GTTAGAGTGG TAGTCTCAGC
GGCCGGGGCA 50
60

(2) INFORMATION FOR SEQ ID NO:254:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 60 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(x1) SEQUENCE DESCRIPTION: SEQ ID NO:254:
GCAGTAGGGA GCAAGCGGGC CTAGGGTAG TGTGATGAT GCGGCGAGGC
GTTCAGACTT 50
60

(2) INFORMATION FOR SEQ ID NO:255:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 59 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(x1) SEQUENCE DESCRIPTION: SEQ ID NO:255:
GAGAGCTGGG GCAGGCTAGG AGTAGGATG GCGAGTGGT AGGCGCGGTT
CGCTGGCA 50
59

(2) INFORMATION FOR SEQ ID NO:256:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 60 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

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(xi) SEQUENCE DESCRIPTION: SEQ ID NO:256:
CTTGGAGAG ACTCCGTGCT AGGGCAGGTT GGGGTACTT CTTGGAAGA
GGAGACGCT

50
60

(2) INFORMATION FOR SEQ ID NO:257:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 60 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:257:
GATGATATAC ACGTGGCCGG GAGCGTGGT AGGTAGGAT GTGTGAGT
GGCCAGCTG

50
60

(2) INFORMATION FOR SEQ ID NO:258:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 60 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:258:
CGAGCCCGG GTAGTGTGG GATCGGGCGG TAGGACATGG CAGTCCGCT
GTACCGCTGG

50
60

(2) INFORMATION FOR SEQ ID NO:259:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 59 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:259:
GCAAGCTTC GATGTAGT GTAGTAGT CTTGGTTGG GTGTGTGCT
CCACTGTC

50
59

(2) INFORMATION FOR SEQ ID NO:260:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 59 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:260:
GAGGTGCGAG AGTACGCTT GTTAGGGTAC GTTGGCTTG AGGAGCCCG
CCTGCTCG

50
59

(2) INFORMATION FOR SEQ ID NO:261:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 60 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:261:
CCTGTAGAG ACGGAGAGA GTAGGGTTG GCGGTAGTC GCAAGGTGCT
50

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AGGCCACTCC

60

(2) INFORMATION FOR SEQ ID NO:262:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 60 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:262:
GAGGGTCA GCGGGGAGC GTGGTAGGA AGGTTGGCT CTTCACGCT
GTTTGGGCC

50
60

(2) INFORMATION FOR SEQ ID NO:263:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 59 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:263:
CAGCATGAG GCGTGGCGA GTGTGTAGG GTAGGTGCT GTGAGAGGAG
CAGGTGGT

50
59

(2) INFORMATION FOR SEQ ID NO:264:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 60 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:264:
GGCTTCGAT GATTCAGCT GTGTAGGCA TTAGAGATG GGGTCTGTG
GACTGGCGCT

50
60

(2) INFORMATION FOR SEQ ID NO:265:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 60 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:265:
GCATAGGGA GATGCGGCG CTAGGTTAG TTGATGAT GCAGGACAGC
GTGCACTT

50
60

(2) INFORMATION FOR SEQ ID NO:266:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 60 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:266:
GATTCGATC ACTTGCGAG ACTTGCTAG GAGGTTGG CCGGTAGGG
CCGTAGCAG

50
60

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- (2) INFORMATION FOR SEQ ID NO:267:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 60 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:267:
GAGAGTTCG TAGGGGTGGT TGGGCTCCG TGAAGTCTGT CGAAGGACAG
GAGGTTCG 50 60
- (2) INFORMATION FOR SEQ ID NO:268:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 60 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:268:
GGAACCGGAG AGGGGTAGG GTTGGAGGGG TTGGCCGATG TGTAGGCAC
GACTGGAT 50 60
- (2) INFORMATION FOR SEQ ID NO:269:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 60 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:269:
TGTTCAGT TGGCGCAG TGTAGGATC AGGATGCGA GCCGAAGAT
GTTCGCCAC 50 60
- (2) INFORMATION FOR SEQ ID NO:270:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 60 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:270:
CGGTAAGTCG GAGGTTCG CTAGCCGCTG GTAGGTTAGG TTGGGCGGCC
TAGCGGGCG 50 60
- (2) INFORMATION FOR SEQ ID NO:271:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 60 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:271:
TGTCTGGC TGTTCGACG GGCTCGTAA GGGAGTTGG GCATCGTAGG
ATGTGCGCG 50 60
- (2) INFORMATION FOR SEQ ID NO:272:
(1) SEQUENCE CHARACTERISTICS:

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- (A) LENGTH: 75 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:272:
AGATCCCTGT CGAGCATGCT ACACCCGTGG TAGGTAGGA TGGGTTGCTC
TAGCTTAAC TCGTTTCTGG ACGGG 50 75
- (2) INFORMATION FOR SEQ ID NO:273:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 75 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:273:
AGATCCCTGT CGAGCATGCT GTGATAGGT AGGTCGAGT GGGCTACGCT
TAGCTTAAC TCGTTTCTGG ACGGG 50 75
- (2) INFORMATION FOR SEQ ID NO:274:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 75 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:274:
AGATCCCTGT CGAGCATGCT GCCGTAACA GGGTAGGTGT GATGCTGCC
TAGCTTAAC TCGTTTCTGG ACGGG 50 75
- (2) INFORMATION FOR SEQ ID NO:275:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 75 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:275:
AGATCCCTGT CGAGCATGCT GTGTGGTAG GGTAGGGAT GGTAGCGGTT
TAGCTTAAC TCGTTTCTGG ACGGG 50 75
- (2) INFORMATION FOR SEQ ID NO:276:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 75 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:276:
AGATCCCTGT CGAGCATGCT GGGAGTGTGA GGAGTAGGT TGAAGCCGTA
TAGCTTAAC TCGTTTCTGG ACGGG 50 75
- (2) INFORMATION FOR SEQ ID NO:277:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 105 base pairs
(B) TYPE: nucleic acid

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- (C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(X1) SEQUENCE DESCRIPTION: SEQ ID NO:277:
AGATGCTGT CGAGCATGCT GGCGGCGTGG GTGAGCTGAGC GCACTGTGCT
TGGGCGGAGA GGTATGAGAGT GCATGATGCGC GTAGCTAAAC TGCTTTGTGC
ACGGG 50
100
105
- (2) INFORMATION FOR SEQ ID NO:278:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 101 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(X1) SEQUENCE DESCRIPTION: SEQ ID NO:278:
AGATGCTGT CGAGCATGCT CTTCGAGAC AGTCGCTGCT AGGCGAGGTT
GGGTGACTT GTGGAAGAA GCGAGACGCT GTAGCTAAAC TGCTTTGTGC
A 50
100
105
- (2) INFORMATION FOR SEQ ID NO:279:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 38 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(X1) SEQUENCE DESCRIPTION: SEQ ID NO:279:
CACTCCGCTG TAGGCGAGCT TGGGCTGACT TCCTGGA 38
- (2) INFORMATION FOR SEQ ID NO:280:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 105 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(X1) SEQUENCE DESCRIPTION: SEQ ID NO:280:
AGATGCTGT CGAGCATGCT GGCGTCCAT GATTCAGGTC GTGGTAGGCA
TTAGGGAATG GGTCTCTGTG GACTGGCCT GTAGCTAAAC TGCTTTGTGC 100
ACGGG 105
- (2) INFORMATION FOR SEQ ID NO:281:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 77 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(X1) SEQUENCE DESCRIPTION: SEQ ID NO:281:
GGAGCTCAG AAUAAAGCU CAUUGCUAU CGCCUACUC GGGGCUCCA
CCUUGACA UGAGGCCCG AUCCGCG 77
- (2) INFORMATION FOR SEQ ID NO:282:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 77 base pairs
(B) TYPE: nucleic acid

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- (C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(X1) SEQUENCE DESCRIPTION: SEQ ID NO:282:
GGAGCTCAG AAUAAAGCU CAUUGCUAU CGCCUACUC GGGGCUCCG
CACUUGACA UGAGGCCCG AUCCGCG 50
77
- (2) INFORMATION FOR SEQ ID NO:283:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 77 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(X1) SEQUENCE DESCRIPTION: SEQ ID NO:283:
GGAGCTCAG AAUAAAGCU CAUUGCGCA GCUACAGAC ACACUCCUG
CACUUGACA UGAGGCCCG AUCCGCG 50
77
- (2) INFORMATION FOR SEQ ID NO:284:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 77 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(X1) SEQUENCE DESCRIPTION: SEQ ID NO:284:
GGAGCTCAG AAUAAAGCU CAUUGAGAC UAUUGGCUCA ACCCGUAGC
UCCUUGACA UGAGGCCCG AUCCGCG 50
77
- (2) INFORMATION FOR SEQ ID NO:285:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 77 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(X1) SEQUENCE DESCRIPTION: SEQ ID NO:285:
GGAGCTCAG AAUAAAGCU CAUUGCGCG GCUUGGAGG CUACCGAGA
CACUUGACA UGAGGCCCG AUCCGCG 50
77
- (2) INFORMATION FOR SEQ ID NO:286:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 77 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(X1) SEQUENCE DESCRIPTION: SEQ ID NO:286:
GGAGCTCAG AAUAAAGCU CAUUGGUCG UACCGAGAC ACACCGAGC
UGUUGACA UGAGGCCCG AUCCGCG 50
77
- (2) INFORMATION FOR SEQ ID NO:287:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 77 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(X1) SEQUENCE DESCRIPTION: SEQ ID NO:287:

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GGAGGCTCAG AAUAAAGCU CAACAGGAC AGCUAACCA GCCACUUGC 50
CCUUCGACA UGAGGCCCG AUCCGCG 77

(2) INFORMATION FOR SEQ ID NO:288:

- (1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 77 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:288:
GGAGGCTCAG AAUAAAGCU CAACAGGAC GUAAACCAAG AUCCGCTGG 50
CGAUUCGACA UGAGGCCCG AUCCGCG 77

(2) INFORMATION FOR SEQ ID NO:289:

- (1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 77 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:289:
GGAGGCTCAG AAUAAAGCU CAACAGGAC UUAACACAGC CACACCTUC 50
UGUUCGACA UGAGGCCCG AUCCGCG 77

(2) INFORMATION FOR SEQ ID NO:290:

- (1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 77 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:290:
GGAGGCTCAG AAUAAAGCU CAACAGGAC CUUCCAGAG CUUCCCTUG 50
UCCUUCGACA UGAGGCCCG AUCCGCG 77

(2) INFORMATION FOR SEQ ID NO:291:

- (1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 77 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:291:
GGAGGCTCAG AAUAAAGCU CAUUCUAU GCGCUAGCUC GCGCUCUUA 50
CCUUCGACA UGAGGCCCG AUCCGCG 77

(2) INFORMATION FOR SEQ ID NO:292:

- (1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 77 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:292:
GGAGGCTCAG AAUAAAGCU CAACUAU GCGCCACCC GCGCUCUCCG 50
ACCUUCGACA UGAGGCCCG AUCCGCG 77

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(2) INFORMATION FOR SEQ ID NO:293:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 76 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:293:
GGAGGCTCAG AAUAAAGCU CAACAGGAC GCGUCAGAC GCACAUCCU 50
GCUUCGACA UGAGGCCCG AUCCGCG 76

(2) INFORMATION FOR SEQ ID NO:294:

- (1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 77 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:294:
GGAGGCTCAG AAUAAAGCU CAACAGGCC CGUCUAAGC UAACCUAGAC 50
CCUUCGACA UGAGGCCCG AUCCGCG 77

(2) INFORMATION FOR SEQ ID NO:295:

- (1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 77 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:295:
GGAGGCTCAG AAUAAAGCU CAAGGUAAC GUUCGACAA GUACACCTUC 50
GCUUCGACA UGAGGCCCG AUCCGCG 77

(2) INFORMATION FOR SEQ ID NO:296:

- (1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 77 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:296:
GGAGGCTCAG AAUAAAGCU CAAGGGACA GCGUACAGAC AAGUGCACCC 50
AACUUCGACA UGAGGCCCG AUCCGCG 77

(2) INFORMATION FOR SEQ ID NO:297:

- (1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 77 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:297:
GGAGGCTCAG AAUAAAGCU CAACGACAG AGCGACCAU UAGCGACGA 50
CACUUCGACA UGAGGCCCG AUCCGCG 77

(2) INFORMATION FOR SEQ ID NO:298:

- (1) SEQUENCE CHARACTERISTICS:

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- (A) LENGTH: 77 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:298:
GGAGGUCGAG AAUAAAGCU CAACUCUCG AAAGCAGCG UGUAGCAAGA
CACUCGACA UGAGGCCCG AUCCGCG
- (2) INFORMATION FOR SEQ ID NO:299:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 77 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:299:
GGAGGUCGAG AAUAAAGCU CAAGUGGA AAAGCUCACU GAACAGACAC
CACUCGACA UGAGGCCCG AUCCGCG
- (2) INFORMATION FOR SEQ ID NO:300:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 77 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:300:
GGAGGUCGAG AAUAAAGCU CAAGCUCAG CUAUAGACAA GUGCAGCUCG
GUUUCGACA UGAGGCCCG AUCCGCG
- (2) INFORMATION FOR SEQ ID NO:301:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 79 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:301:
GGAGGAGCC UGUGAGCAU GUGAGCCG AGUAAAGCA UGAAGUGCAC
AUAGGAGCU AAACAGCUCU GUGACGCG
- (2) INFORMATION FOR SEQ ID NO:302:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 79 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:302:
GGAGGAGCC UGUGAGCAU GUGAGCCG AGUAAAGCA CCGGCGAGAC
CAUUGAGCU AAACAGCUCU GUGACGCG

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- (C) STRANDEDNESS: single
(D) TOPOLOGY: linear
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:303:
GGAGGAGCC UGUGAGCAU GUGAGCAGC UUGGUAAGC UAUCGACAG
UUAAGGAGCU AAACAGCUCU GUGACGCG
- (2) INFORMATION FOR SEQ ID NO:304:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 79 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:304:
GGAGGAGCC UGUGAGCAU GUGAGAGGG AAAGGUDAG UCCGGUACAC
CUUGGAGCU AAACAGCUCU GUGACGCG
- (2) INFORMATION FOR SEQ ID NO:305:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 79 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:305:
GGAGGAGCC UGUGAGCAU GUGAGGUA AGGUAUCGAC AAAGCUCACU
CAAGGAGCU AAACAGCUCU GUGACGCG
- (2) INFORMATION FOR SEQ ID NO:306:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 79 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:306:
GGAGGAGCC UGUGAGCAU GUGAGGUA AGGUAACACA AAACACUCC
AACGAGAGCU AAACAGCUCU GUGACGCG
- (2) INFORMATION FOR SEQ ID NO:307:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 79 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:307:
GGAGGAGCC UGUGAGCAU GUGAGGUA CCGGAGUCA AGUGCAGUCG
ACAUAGAGCU AAACAGCUCU GUGACGCG
- (2) INFORMATION FOR SEQ ID NO:308:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 79 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

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- (x1) SEQUENCE DESCRIPTION: SEQ ID NO:308:
GGAGAGGCC UGUGAGCAU GCUGGGAAA CGCUAUCGAC GAGUGCACCC 50
GGCGUAGCU AAACAGCUU GUCCACGGG 79
- (2) INFORMATION FOR SEQ ID NO:309:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 79 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(x1) SEQUENCE DESCRIPTION: SEQ ID NO:309:
GGAGAGGCC UGUGAGCAU GCUCCGAGG GUACGUGGG GUCCAGCACCA 50
CCUGUAGCU AAACAGCUU GUCCACGGG 79
- (2) INFORMATION FOR SEQ ID NO:310:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 79 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(x1) SEQUENCE DESCRIPTION: SEQ ID NO:310:
GGAGAGGCC UGUGAGCAU GCUUGCGGG UAACTUATUG GCAGAGGCACC 50
CGCGUAGCU AAACAGCUU GUCCACGGG 79
- (2) INFORMATION FOR SEQ ID NO:311:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 79 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(x1) SEQUENCE DESCRIPTION: SEQ ID NO:311:
GGAGAGGCC UGUGAGCAU GCUUGGUAC GCUUGAGACA AGUGCACCCAG 50
CGCGUAGCU AAACAGCUU GUCCACGGG 79
- (2) INFORMATION FOR SEQ ID NO:312:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 79 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(x1) SEQUENCE DESCRIPTION: SEQ ID NO:312:
GGAGAGGCC UGUGAGCAU GCUAGGGUA ACGUACUGGC AAGCUCACCT 50
CGCGUAGCU AAACAGCUU GUCCACGGG 79
- (2) INFORMATION FOR SEQ ID NO:313:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 79 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(x1) SEQUENCE DESCRIPTION: SEQ ID NO:313:
GGAGAGGCC UGUGAGCAU GCUAGGGUA ACGUAGAGC AAGAACACTUC 50

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- AGUGUAGCU AAACAGCUU GUCCACGGG 79
- (2) INFORMATION FOR SEQ ID NO:314:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 79 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(x1) SEQUENCE DESCRIPTION: SEQ ID NO:314:
GGAGAGGCC UGUGAGCAU GCUAGGGUA CGCUAUGGCA AAGACCCAG 50
CCCUGUAGCU AAACAGCUU GUCCACGGG 79
- (2) INFORMATION FOR SEQ ID NO:315:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 79 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(x1) SEQUENCE DESCRIPTION: SEQ ID NO:315:
GGAGAGGCC UGUGAGCAU GCUAGGAAA ACGUACGUC GAGCCACTCC 50
AUGCGUAGCU AAACAGCUU GUCCACGGG 79
- (2) INFORMATION FOR SEQ ID NO:316:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 79 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(x1) SEQUENCE DESCRIPTION: SEQ ID NO:316:
GGAGAGGCC UGUGAGCAU GCUAGGAAA CCGUAGAGCA AGUGCACTGG 50
ACAUGUAGCU AAACAGCUU GUCCACGGG 79
- (2) INFORMATION FOR SEQ ID NO:317:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 79 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(x1) SEQUENCE DESCRIPTION: SEQ ID NO:317:
GGAGAGGCC UGUGAGCAU GCUAGGGUA CCGUAGACA GATCACCCAG 50
UUGGUGUAGCU AAACAGCUU GUCCACGGG 79
- (2) INFORMATION FOR SEQ ID NO:318:
(A) LENGTH: 79 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(x1) SEQUENCE DESCRIPTION: SEQ ID NO:318:
GGAGAGGCC UGUGAGCAU GCUAGGACG GCAAGCGUC UGACCAAGUC 50
ACUUGUAGCU AAACAGCUU GUCCACGGG 79
- (2) INFORMATION FOR SEQ ID NO:319:

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(A) LENGTH: 77 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(X1) SEQUENCE DESCRIPTION: SEQ ID NO:319:
GGAGGCTCAG AAUAAAGCG CAUAGGAGUC UAAACACACAC ACACUCAGGC
UUUUUACAC UGAGCCCCG AUCCGCG 50

(2) INFORMATION FOR SEQ ID NO:320:
(A) LENGTH: 66 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(X1) SEQUENCE DESCRIPTION: SEQ ID NO:320:
CGAGCAGCGU GNNNNNNNNN NNNNNNNNNN NGUAGCTAAA
CAGCUCUUGC GACGCG 66

(2) INFORMATION FOR SEQ ID NO:321:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(X1) SEQUENCE DESCRIPTION: SEQ ID NO:321:
ATCCGCTCA TTACGATAC T 21

(2) INFORMATION FOR SEQ ID NO:322:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 86 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(X1) SEQUENCE DESCRIPTION: SEQ ID NO:322:
ATCCGCTCA TTACGATAC TNNNNNNNNN NNNNNNNNNN NNNNNNNNNN
NNNNNNNNN NACTTAGACA AAATCACCTG CAGGCG 50

(2) INFORMATION FOR SEQ ID NO:323:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 28 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(X) FEATURE:
(A) NAME/KEY: N
(B) LOCATION: 26-28
(D) OTHER INFORMATION: The N = biotin
(X1) SEQUENCE DESCRIPTION: SEQ ID NO:323:
TGAACGTGT TTATGAGAGC TCCCCNNN 28

(2) INFORMATION FOR SEQ ID NO:324:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs

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(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(X1) SEQUENCE DESCRIPTION: SEQ ID NO:324:
CTACCTAACG TGTGACTACG 20

(2) INFORMATION FOR SEQ ID NO:325:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 81 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(X1) SEQUENCE DESCRIPTION: SEQ ID NO:325:
CTACCTACAGT CTGACTACG NNNNNNNNNN NNNNNNNNNN NNNNNNNNNN
NNNNNNNNN TAGTACTC TCATGTATTC C 81

(2) INFORMATION FOR SEQ ID NO:326:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 25 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(X) FEATURE:
(A) NAME/KEY: N
(B) LOCATION: 22 and 24
(D) OTHER INFORMATION: The N = biotin
(X1) SEQUENCE DESCRIPTION: SEQ ID NO:326:
ATCGATGAG AGTACATAG GNNNA 25

(2) INFORMATION FOR SEQ ID NO:327:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(X1) SEQUENCE DESCRIPTION: SEQ ID NO:327:
GGAGGACGA TGGCG 15

(2) INFORMATION FOR SEQ ID NO:328:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 61 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(X1) SEQUENCE DESCRIPTION: SEQ ID NO:328:
GGAGGACGA TGGCGNNNNN NNNNNNNNNN NNNNNNNNNN NNNNNNNNNN
GACGAGCGG A 61

(2) INFORMATION FOR SEQ ID NO:329:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid

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(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(1x) FEATURE:
(A) NAME/KEY: N
(B) LOCATION: 17 and 19
(D) OTHER INFORMATION: The N = biotin
(x1) SEQUENCE DESCRIPTION: SEQ ID NO:329:
GTGTGCTGCT GCCCTTANA 20

(2) INFORMATION FOR SEQ ID NO:330:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 86 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(x1) SEQUENCE DESCRIPTION: SEQ ID NO:330:
ATCCGCTGA TTAGCGATAC TGACGACATTA GGGCTATGCG AAATCCGACT
ATCAGAAAGCG TACTTGAGCA AAATCACCCTG CAGGGG 50
86

(2) INFORMATION FOR SEQ ID NO:331:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 85 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(x1) SEQUENCE DESCRIPTION: SEQ ID NO:331:
ATCCGCTGA TTAGCGATAC TAGGCGAGG GCTATGCAAA TCGGCGCGCC
TATGGCCATT ACTGAGCAA AATCACCCTG AGGGG 50
85

(2) INFORMATION FOR SEQ ID NO:332:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 84 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(x1) SEQUENCE DESCRIPTION: SEQ ID NO:332:
ATCCGCTGA TTAGCGATAC TAGGCGAGG CTAATCAAAAT CGCGCGCGCT
ATGGCATTTA CTTAGCAAAA ATCACCCTGA GGGG 50
84

(2) INFORMATION FOR SEQ ID NO:333:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 84 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(x1) SEQUENCE DESCRIPTION: SEQ ID NO:333:
ATCCGCTGA TTAGCGATAC TCGGCGAGG TATGCAAAAT CGCGCGCGCTA
TGGCATTGA CTTAGCAAAA ATCACCCTGA GGGG 50
84

(2) INFORMATION FOR SEQ ID NO:334:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 86 base pairs

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(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(x1) SEQUENCE DESCRIPTION: SEQ ID NO:334:
ATCCGCTGA TTAGCGATAC TAGGCGCTGT GCAACCAATG GCGACCATCG
GAATCCGTGC TACTTGAGCA AAATCACCCTG CAGGGG 50
86

(2) INFORMATION FOR SEQ ID NO:335:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 86 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(x1) SEQUENCE DESCRIPTION: SEQ ID NO:335:
ATCCGCTGA TTAGCGATAC TAGGCGCTGT GCAACCAATG GCGACCATCG
GAATCCGTGC TACTTGAGCA AAATCACCCTG CAGGGG 50
86

(2) INFORMATION FOR SEQ ID NO:336:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(x1) SEQUENCE DESCRIPTION: SEQ ID NO:336:
ATCCGCTGA TTAGCGATAC TGCTTCGGG GCTTTGCAAA AATGCTAGA
CTTACAGAGC AGACTTGAC AAATCACCCTG CAGGGG 50
87

(2) INFORMATION FOR SEQ ID NO:337:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(x1) SEQUENCE DESCRIPTION: SEQ ID NO:337:
ATCCGCTGA TTAGCGATAC TCGTTCCTTA TAGGCGCTTT GCAAAATGCT
ATTAATCGTA CTAATTGAC AAATCACCCTG CAGGGG 50
87

(2) INFORMATION FOR SEQ ID NO:338:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 86 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(x1) SEQUENCE DESCRIPTION: SEQ ID NO:338:
ATCCGCTGA TTAGCGATAC TCAAGGGCT TTCAAAATG ACAACCTTA
AGCTTACAC TACTTGAGCA AAATCACCCTG CAGGGG 50
86

(2) INFORMATION FOR SEQ ID NO:339:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 86 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single

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- (D) TOPOLOGY: linear
(X1) SEQUENCE DESCRIPTION: SEQ ID NO:339:
ATCCGCTCA TTAGCCTAC TAGTGAGGCT ATGCAATTA TCGCCTAGTG
GCTGATACA CACTGAGA AAATCACCTG CAGGGG 50 86
- (2) INFORMATION FOR SEQ ID NO:340:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(X1) SEQUENCE DESCRIPTION: SEQ ID NO:340:
RGGGCTTTC AAAN 14
- (2) INFORMATION FOR SEQ ID NO:341:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 35 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(X1) SEQUENCE DESCRIPTION: SEQ ID NO:341:
AGCCAGGAG TATGCAATC GCGGCGCCTA TGGCC 35
- (2) INFORMATION FOR SEQ ID NO:342:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 82 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(X1) SEQUENCE DESCRIPTION: SEQ ID NO:342:
CTACCTACGA TCTGACTAGC AGGCTTGT AAACATGAGC TAGCTTACT
ATGCAGGCA TAGCTTACT TCAATTAFTT CC 50 82
- (2) INFORMATION FOR SEQ ID NO:343:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 82 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(X1) SEQUENCE DESCRIPTION: SEQ ID NO:343:
CTACCTACGA TCTGACTAGC TAGCGGGCT TTGCAAAAAA CAGTTGTAG
TTCTAAGCA TAGCTTACT TCAATTAFTT CC 50 82
- (2) INFORMATION FOR SEQ ID NO:344:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 82 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(X1) SEQUENCE DESCRIPTION: SEQ ID NO:344:
CTACCTACGA TCTGACTAGC AGGCTTGT AAACATGAGC TAGCTTACT
ATGCAGGCA TAGCTTACT TCAATTAFTT CC 50 82

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- (2) INFORMATION FOR SEQ ID NO:345:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 81 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(X1) SEQUENCE DESCRIPTION: SEQ ID NO:345:
CTACCTACGA TCTGACTAGC AGGCTTGT AAACATGAGC TAGCTTACT
ATGCAGGCA TAGCTTACT TCAATTAFTT C 50 81
- (2) INFORMATION FOR SEQ ID NO:346:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 79 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(X1) SEQUENCE DESCRIPTION: SEQ ID NO:346:
CTACCTACGA TCTGACTAGC GGGCTCTGC AAATCTGAA ATGACACCC
CAGTCTGAG CTATCTCTCA TGTATFTTCC 50 79
- (2) INFORMATION FOR SEQ ID NO:347:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 62 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(X1) SEQUENCE DESCRIPTION: SEQ ID NO:347:
CTACCTACGA TCTGACTAGC AGGCTTGT AAACATGAGC TAGCTTACT
TCAATTAFTT CC 50 62
- (2) INFORMATION FOR SEQ ID NO:348:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 79 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(X1) SEQUENCE DESCRIPTION: SEQ ID NO:348:
CTACCTACGA TCTGACTAGC AGGCTTGT AAACATGAGC TAGCTTACT
ATGCAGGCA TAGCTTACT TCAATTAFTT CC 50 79
- (2) INFORMATION FOR SEQ ID NO:349:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 76 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(X1) SEQUENCE DESCRIPTION: SEQ ID NO:349:
CTACCTACGA TCTGACTAGC GCGGCGGCGC TTGCAAAAT CAGCTTACT
GATTAGCT ACTCTAGT APTTCC 50 76
- (2) INFORMATION FOR SEQ ID NO:350:
(1) SEQUENCE CHARACTERISTICS:

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(A) LENGTH: 76 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(x1) SEQUENCE DESCRIPTION: SEQ ID NO:350:
CTACCTACGA TCTGACTAGC AGGCGTTGT AAACATGAC TACCTACCT
ATGCTAGCT ACTCATGT AATTCC

50
76

(2) INFORMATION FOR SEQ ID NO:351:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(x1) SEQUENCE DESCRIPTION: SEQ ID NO:351:
GCRGGGCTT GYAAN

16

(2) INFORMATION FOR SEQ ID NO:352:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 61 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(x1) SEQUENCE DESCRIPTION: SEQ ID NO:352:
GGAGAGACA TCGGGGGGC TTGCAGAA TTGTTAATC TACCCAGAC
GACGACGGG A

50
61

(2) INFORMATION FOR SEQ ID NO:353:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 61 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(x1) SEQUENCE DESCRIPTION: SEQ ID NO:353:
GGAGAGACA TCGGGGGCTA TGTAAATAC TGTCTACTA CGCATCAGAC
GACGACGGG A

50
61

(2) INFORMATION FOR SEQ ID NO:354:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 62 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(x1) SEQUENCE DESCRIPTION: SEQ ID NO:354:
GGAGAGACA TCGGGGGGG GCTCTGAAA GTCTTCAAC TACCACGAGA
CGACGCGG A

50
62

(2) INFORMATION FOR SEQ ID NO:355:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 61 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single

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(D) TOPOLOGY: linear
(x1) SEQUENCE DESCRIPTION: SEQ ID NO:355:
GGAGAGACA TCGGGGGGCT CTGCAGAGTG AAATCCGAC TACCGAGAC
GACGACGGG A

50
61

(2) INFORMATION FOR SEQ ID NO:356:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 61 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(x1) SEQUENCE DESCRIPTION: SEQ ID NO:356:
GGAGAGACA TCGGGGGGGC TCTGCAGAT TTGTTAATC ACTGACAGAC
GACGACGGG A

50
61

(2) INFORMATION FOR SEQ ID NO:357:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 61 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(x1) SEQUENCE DESCRIPTION: SEQ ID NO:357:
GGAGAGACA TCGGGGGGCTA GCTACGGGGG CTTGTMAAA CCCCCAGAC
GACGACGGG A

50
61

(2) INFORMATION FOR SEQ ID NO:358:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 61 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(x1) SEQUENCE DESCRIPTION: SEQ ID NO:358:
GGAGAGACA TCGGGGGCT ATGCAGATTT TCCAACTAC TGCATCAGAC
GACGACGGG A

50
61

(2) INFORMATION FOR SEQ ID NO:359:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 61 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(x1) SEQUENCE DESCRIPTION: SEQ ID NO:359:
GGAGAGACA TCGGGGGCTA GTACCGGGG CTTGTMAAA CCCCCAGAC
GACGACGGG A

50
61

(2) INFORMATION FOR SEQ ID NO:360:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 61 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(x1) SEQUENCE DESCRIPTION: SEQ ID NO:360:

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GGAGAGACGA TGGGGGGGCTC TGCAGAGAC ACAGGTCTCA CGCATCAGAC 50
GACGACGGGG A 61

(2) INFORMATION FOR SEQ ID NO:361:

- (1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 61 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(x1) SEQUENCE DESCRIPTION: SEQ ID NO:361:
GGAGAGACGA TGGGGGGGCTC TGCAGATCCT CTTGGGAGAG CTACGCGAGAC 50
GACGACGGGG A 61

(2) INFORMATION FOR SEQ ID NO:362:

- (1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 61 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(x1) SEQUENCE DESCRIPTION: SEQ ID NO:362:
GGAGAGACGA TGGGGGGGCTC TGTAAATCT CATCTGAGAC TACGTCAGAC 50
GACGACGGGG A 61

(2) INFORMATION FOR SEQ ID NO:363:

- (1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(x1) SEQUENCE DESCRIPTION: SEQ ID NO:363:
SSGGGGCTNT GCAAN 16

(2) INFORMATION FOR SEQ ID NO:364:

- (1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 35 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(x1) SEQUENCE DESCRIPTION: SEQ ID NO:364:
GCGGGGCTAC GTACGGGGGC TTGTAAAC CCGGC 35

(2) INFORMATION FOR SEQ ID NO:365:

- (1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 35 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(x1) SEQUENCE DESCRIPTION: SEQ ID NO:365:
GCGGGGCTAT GTAAATCT GCTGTACTAC GCATC 35

(2) INFORMATION FOR SEQ ID NO:366:

- (1) SEQUENCE CHARACTERISTICS:

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- (A) LENGTH: 86 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(x1) SEQUENCE DESCRIPTION: SEQ ID NO:366:
ATCCGCTGGA TTAGGATAC TGCTCCCA CGAGCGTAG TGCACAGAC 50
CCCATGTGA TACTTGACA AATCACTGC CAGGG 86

(2) INFORMATION FOR SEQ ID NO:367:

- (1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 86 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(x1) SEQUENCE DESCRIPTION: SEQ ID NO:367:
ATCCGCTGGA TTAGGATAC TGACCAAGC TGATGCTGC CTTCCGATC 50
GGCAGTTACC CACTTGAGA AATCACTGC CAGGG 86

(2) INFORMATION FOR SEQ ID NO:368:

- (1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 86 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(x1) SEQUENCE DESCRIPTION: SEQ ID NO:368:
ATCCGCTGGA TTAGGATAC TGACCAAGC TGATGCTGC CTTCCGATC 50
GGCAGTTACT CACTTGAGA AATCACTGC CAGGG 86

(2) INFORMATION FOR SEQ ID NO:369:

- (1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 85 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(x1) SEQUENCE DESCRIPTION: SEQ ID NO:369:
ATCCGCTGGA TTAGGATAC TTAACTACT CAATGGGCA GGTCCGATC 50
CTCCGATC ACTTGAGA AATCACTGC AAGGG 85

(2) INFORMATION FOR SEQ ID NO:370:

- (1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 85 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(x1) SEQUENCE DESCRIPTION: SEQ ID NO:370:
ATCCGCTGGA TTAGGATAC TGACCAAGC TGATGCTGC CTTCCGATC 50
GGCTTACC ACTTGAGA AATCACTGC AAGGG 85

(2) INFORMATION FOR SEQ ID NO:371:

- (1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 85 base pairs
(B) TYPE: nucleic acid

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- (C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(X1) SEQUENCE DESCRIPTION: SEQ ID NO:371:
ATCGGCTGA TTAGCGATAC TTACACACT CAATGGGCA CGTCCGAG
CTCCGAGTC ACTTGAGCA AATCACCCTG AGGGG 50
- (2) INFORMATION FOR SEQ ID NO:372:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 86 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(X1) SEQUENCE DESCRIPTION: SEQ ID NO:372:
ATCGGCTGA TTAGCGATAC TGACACGAC TGATGGCTG CTTCCCGATA
GGCAGTTAC CACTGAGCA AATCACCCTG CAGGGG 86
- (2) INFORMATION FOR SEQ ID NO:373:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 85 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(X1) SEQUENCE DESCRIPTION: SEQ ID NO:373:
ATCGGCTGA TTAGCGATAC TGACACGAC TGAATGCGTC GCCTCCCAT
AGCAGTTCC ACTTGAGCA AATCACCCTG AGGGG 85
- (2) INFORMATION FOR SEQ ID NO:374:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 86 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(X1) SEQUENCE DESCRIPTION: SEQ ID NO:374:
ATCGGCTGA TTAGCGATAC TGCTTCCGA CGAGGCTTG TCACACGAC
CCCATGGGA TACTGAGCA AATCACCCTG CAGGGG 86
- (2) INFORMATION FOR SEQ ID NO:375:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 86 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(X1) SEQUENCE DESCRIPTION: SEQ ID NO:375:
ATCGGCTGA TTAGCGATAC TGACACGAC TGATGGCTG CTTCCCGATA
GGCAGTTAC CACTGAGCA AATCACCCTG CAGGGG 86

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- (X1) SEQUENCE DESCRIPTION: SEQ ID NO:376:
ATCGGCTGA TTAGCGATAC TACACGGTC TGCTGACAC CCTGTACTA
ACGTTACG TACTGAGCA AATCACCCTG CAGGGG 86
- (2) INFORMATION FOR SEQ ID NO:377:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(X1) SEQUENCE DESCRIPTION: SEQ ID NO:377:
ATCGGCTGA TTAGCGATAC TTGTGCTCG GGAAGATTG GCTACGAC
GGGTTACT ACACCTGAGC AATCACCCT GAGGGG 87
- (2) INFORMATION FOR SEQ ID NO:378:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 71 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(X1) SEQUENCE DESCRIPTION: SEQ ID NO:378:
CTACCTAGA TCTGACTAGC TGAAGCGCT CTTGACAGT TTCTGAGAGT
AGCTTACT CATGTAFTT C 71
- (2) INFORMATION FOR SEQ ID NO:379:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 82 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(X1) SEQUENCE DESCRIPTION: SEQ ID NO:379:
CTACCTAGA TCTGACTAGC TGAAGCGCT CTTGACAGT TTCTGAGAGC
TCTCAGCA TACTTACTC TCAITGATTT CC 82
- (2) INFORMATION FOR SEQ ID NO:380:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 82 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(X1) SEQUENCE DESCRIPTION: SEQ ID NO:380:
CTACCTAGA TCTGACTAGC TGAAGCGCT CTTGACAGT TTCTGAGAGC
TCTCAGCA TACTTACTC TCAITGATTT CC 82
- (2) INFORMATION FOR SEQ ID NO:381:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 82 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(X1) SEQUENCE DESCRIPTION: SEQ ID NO:381:
CTACCTAGA TCTGACTAGC GAGGAACTT CAGTGACA GCAATCCGTT 50

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CGACGANGTA TAGCTTACTC TCATGTATTT CC

82

(2) INFORMATION FOR SEQ ID NO:382:

(1) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 82 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(x1) SEQUENCE DESCRIPTION: SEQ ID NO:382:

CTTACTTACGA TCTGACTAGC ACAGAGAGTT TTACGCGCCAC AGTGAAAGCG

50

GTTGACTTAT TAGCTTACTC TCATGTATTT CC

82

(2) INFORMATION FOR SEQ ID NO:383:

(1) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 70 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(x1) SEQUENCE DESCRIPTION: SEQ ID NO:383:

CTTACTTACGA TCTGACTAGC TCGAGGCGTT CCTGAGCAGT TTCTGAGATA

50

GCTTACTCTC ATGTATTTCC

70

(2) INFORMATION FOR SEQ ID NO:384:

(1) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 61 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(x1) SEQUENCE DESCRIPTION: SEQ ID NO:384:

GGAGGACGA TCGGACGAT AGACGTGAG GATCTTTAG TCCACAGAC

50

GACGACGGGG A

61

(2) INFORMATION FOR SEQ ID NO:385:

(1) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 61 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(x1) SEQUENCE DESCRIPTION: SEQ ID NO:385:

GGGAGACGA TCGGACGAG NGCAGGGCAC AAATCGGATC CTCGTACAGC

50

GACGACGGGG A

61

(2) INFORMATION FOR SEQ ID NO:386:

(1) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 61 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(x1) SEQUENCE DESCRIPTION: SEQ ID NO:386:

GGGAGACGA TCGGACGAG GAGCTTTAG CCGCGCAGAA CAAACGAGAC

50

GACGACGGGG A

61

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(2) INFORMATION FOR SEQ ID NO:387:

(1) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 61 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(x1) SEQUENCE DESCRIPTION: SEQ ID NO:387:

GGAGGACGA TCGGCGCGCA GGAGCTTTAG CCGCACAGT TTGTACAGC

50

GACGACGGGG A

61

(2) INFORMATION FOR SEQ ID NO:388:

(1) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 61 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(x1) SEQUENCE DESCRIPTION: SEQ ID NO:388:

GGGAGACGA TCGGAGAGA GCTTTACGCG CGCCGAGGG GCATCCAGAC

50

GACGACGGGG A

61

(2) INFORMATION FOR SEQ ID NO:389:

(1) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 61 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(x1) SEQUENCE DESCRIPTION: SEQ ID NO:389:

GGGAGACGA TCGGCGCACT GTACAGCTTA GTCACTCTTG CTTCACAGC

50

GACGACGGGG A

61

(2) INFORMATION FOR SEQ ID NO:390:

(1) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 22 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(x1) SEQUENCE DESCRIPTION: SEQ ID NO:390:

CGAGGAT-YT TYATGCGCAGC RG

22

(2) INFORMATION FOR SEQ ID NO:391:

(1) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 25 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(x1) SEQUENCE DESCRIPTION: SEQ ID NO:391:

CGAGGAT-CT TTAGCGCCAC AGGTT

25

(2) INFORMATION FOR SEQ ID NO:392:

(1) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 85 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

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- (D) TOPOLOGY: linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:392:
ATCCGCTGA TTAGGATAC TTGATGATC GTTCACCTCG ACCTAGGTC 50
CACTTGAAAT ACTTAGACA AATCACCTG AGGGG 85
- (2) INFORMATION FOR SEQ ID NO:393:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 86 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:393:
ATCCGCTGA TTAGGATAC TGCAGGCA CTTGGCTCG TTAAATGTT 50
CGCTGCACA TACTTAGCA AATCACCTG CAGGG 86
- (2) INFORMATION FOR SEQ ID NO:394:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 86 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:394:
ATCCGCTGA TTAGGATAC TACAGGCA CCGGTACAT AGGTGCTT 50
AAATGACAC GACTTAGCA AATCACCTG CAGGG 86
- (2) INFORMATION FOR SEQ ID NO:395:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 86 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:395:
ATCCGCTGA TTAGGATAC TGTGCTG CGTCACCTG GTCGAAACC 50
CAGTAACCT AACTTAGCA AATCACCTG CAGGG 86
- (2) INFORMATION FOR SEQ ID NO:396:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 86 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:396:
ATCCGCTGA TTAGGATAC TGTGCTG CGTCACCTG GTTGAACC 50
CAGTAACCT AACTTAGCA AATCACCTG CAGGG 86
- (2) INFORMATION FOR SEQ ID NO:397:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 86 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:397:

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- ATCCGCTGA TTAGGATAC TCAGATGC AAGATCTCG GCGGTGTA 50
TCCCATATG TACTTAGCA AATCACCTG CAGGG 86
- (2) INFORMATION FOR SEQ ID NO:398:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 86 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:398:
ATCCGCTGA TTAGGATAC TGCAGGCA CTTGGCTCG TTAAATGTT 50
CGCTGCACA TACTTAGCA AATCACCTG CAGGG 86
- (2) INFORMATION FOR SEQ ID NO:399:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 80 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:399:
CTACCTAGA TCTGACTAG CTACACATG TGCAGGCTT GCAGCCAC 50
TGGGTGTA GCTTACTC ATGATTC 80
- (2) INFORMATION FOR SEQ ID NO:400:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 82 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:400:
CTACCTAGA TCTGACTAG CTGACTACT GTGCGTCAC CTCGCTGAA 50
ATCGAGTT TACTTACT TCATGATTC CC 82
- (2) INFORMATION FOR SEQ ID NO:401:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 82 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:401:
CTACCTAGA TCTGACTAG CACTCGG AACACCCAG AAGTCCCTC 50
GGTCACTG TACTTACT TCATGATTC CC 82
- (2) INFORMATION FOR SEQ ID NO:402:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 63 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:402:
CTACCTAGA TCTGACTAG ACTGCACC GTTAGAGG CTACTTACT 50
CTCATGATTC TC 63

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- (2) INFORMATION FOR SEQ ID NO:403:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 82 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:403:
CTACTACACA TTGACTAGC ACTAGTAGCC CAGAGTGCCC TCGCCGCTG
AATCGAGCA TAGCTACTC TCATGATTT CC 50 82
- (2) INFORMATION FOR SEQ ID NO:404:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 61 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:404:
GGAGAGACA TCGGCTCCG GGTATAGGC CTAGGGTTTC GTTACCAAGC
GACGACGGG A 50 61
- (2) INFORMATION FOR SEQ ID NO:405:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 61 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:405:
GGAGAGACA TCGGCTCCG GCGATTCTT TGGCACTCTC AGTAAAGAC
GACGACGGG A 50 61
- (2) INFORMATION FOR SEQ ID NO:406:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 61 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:406:
GGAGAGACA TCGGCTCCG GTTTGGGCA TAGGGGCAAC ACATACAGAC
GACGACGGG A 50 61
- (2) INFORMATION FOR SEQ ID NO:407:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 60 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:407:
GGAGAGACA TCGGCTCCG GACCGGGTA CAAGGCATAG GTTACAGAC
ACGACGGGGA 50 60
- (2) INFORMATION FOR SEQ ID NO:408:
(1) SEQUENCE CHARACTERISTICS:

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- (A) LENGTH: 60 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:408:
GGAGAGACA TCGGCTCCG ACATCAGGT GCAAGGCTG GGTCCAGAC
ACGACGGGGA 50 60
- (2) INFORMATION FOR SEQ ID NO:409:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 61 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:409:
GGAGAGACA TCGGCTCCG CGTTGTTCA AGTCGACTC CCTCCAGAC
ACGACGGGGA T 50 61
- (2) INFORMATION FOR SEQ ID NO:410:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 86 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:410:
ATCCGCTGGA TTAGGATAC TTAGCAACT CGGCGTTCC ACGGCAATC
GGTAAATCC CACTTGACA AATCACCCTG CAGGGG 50 86
- (2) INFORMATION FOR SEQ ID NO:411:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 86 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:411:
ATCCGCTGGA TTAGGATAC TTAGCAACT CGGCGTTCC ACGGCAATC
GGTAAATCC CACTTGACA AATCACCCTG CAGGGG 50 86
- (2) INFORMATION FOR SEQ ID NO:412:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 60 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:412:
CTACTACACA TTGACTAGC AAGGATGTA ACACTTACCA TCGAGTCC
GCCAAACAG 50 60
- (2) INFORMATION FOR SEQ ID NO:413:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 82 base pairs
(B) TYPE: nucleic acid

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(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:413:
CTACTTACGA TCTGACTAGC ATACTGACG ATTAGCTCG AAGATCTGCG
GAGTACGAT TAGTACTAC TCATGATTT CC

50
82

(2) INFORMATION FOR SEQ ID NO:414:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 76 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:414:
CTACTTACGA TCTGACTAGC CACTGACATG GAGATACCGA CTCGATTTGT
ATGTTAGCTT ACTCTCAGT APTTCC

50
76

(2) INFORMATION FOR SEQ ID NO:415:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 80 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:415:
CTACTTACGA TCTGACTAGC CACTGACATG GAGATACCGA CTCGATTTGT
ATGTTAGCTT GCTTACTCTC ATGTAATTTCC

50
80

(2) INFORMATION FOR SEQ ID NO:416:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 61 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:416:
GGAGAGACGA TCGGGGCGAC TGTATCCCA CGGATGACAC TCTGGCAGAC
GACGACGGG A

50
61

(2) INFORMATION FOR SEQ ID NO:417:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 61 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:417:
GGAGAGACGA TCGGGGCGAC GGAGACGACG GAAATTTCCA CAGCGCAGAC
GACGACGGG A

50
61

(2) INFORMATION FOR SEQ ID NO:418:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 63 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

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(xi) SEQUENCE DESCRIPTION: SEQ ID NO:418:
GGAGAGACGA TCGGGGCGAC TAGCGGAAGG GAAATTTCCA CAAATCATCAG
ACGACGACG GGA

50
63

(2) INFORMATION FOR SEQ ID NO:419:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 61 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:419:
GGAGAGACGA TCGGGGCGAG AGCGGAGACA CACTCGAATG TTCAACAGAC
GACGACGGG A

50
61

(2) INFORMATION FOR SEQ ID NO:420:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 37 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:420: (1) SEQUENCE
GCGGGGCTCT GCGAAGACGA CAGTCTCTAC GCATCAG

37

(2) INFORMATION FOR SEQ ID NO:421:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 62 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:421:
GGAGAGACGA TCGGGGCGAG TGGGGGGATC ATCAGGGGGTT TGTGACAGA
CGACGACGGG GA

50
62

(2) INFORMATION FOR SEQ ID NO:422:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 61 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:422:
GGAGAGACGA TCGGGGCGAG TAGCGGAAGG GAATTCAGC AACTCATGAC
GACGACGGG A

50
61

(2) INFORMATION FOR SEQ ID NO:423:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 86 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:423:
ATGCCCTGGA TTAGGATAC TACACCAAC CCCCTAAGAT TTTAGACGAA
CTGCGCGGAA CACTTGACA AATTCACCTG CAGGGG

50
86

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- (2) INFORMATION FOR SEQ ID NO:424:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 88 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(x1) SEQUENCE DESCRIPTION: SEQ ID NO:424:
ATCGCCCTGA TTAGCAGTAC TGAAGAGTA GAGGCGCAT CGCTCCGTAT
CAGGTCACT AGACTTGG CAAATCACC TGCAGGGG 50 88
- (2) INFORMATION FOR SEQ ID NO:425:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 86 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(x1) SEQUENCE DESCRIPTION: SEQ ID NO:425:
ATCGCCCTGA TTAGCAGTAC TGAAGAGTA GAGGCGCAT CGCTCCGTAT
CAGGTCACT AGACTTGG CAAATCACC TGCAGGGG 50 86
- (2) INFORMATION FOR SEQ ID NO:426:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 82 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(x1) SEQUENCE DESCRIPTION: SEQ ID NO:426:
CTACTACGA TGTGACTAGC CACCGAAGT TGGATGAGGG TAGGTCAAG
TGGGTATCC TAGCTTACTC TCATGTATTT CC 50 82
- (2) INFORMATION FOR SEQ ID NO:427:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 82 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(x1) SEQUENCE DESCRIPTION: SEQ ID NO:427:
CTACTACGA TGTGACTAGC CACCGAAGT TGGATGAGGG TAGGTCAAG
TGGGTATCC TAGCTTACTC TCATGTATTT CC 50 82
- (2) INFORMATION FOR SEQ ID NO:428:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 61 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(x1) SEQUENCE DESCRIPTION: SEQ ID NO:428:
GGAGAGACA TGGGACAGG GCTATCGGA GGAATCACTT CCGCCAGAC
GACGACGGGG A 50 61
- (2) INFORMATION FOR SEQ ID NO:429:
(1) SEQUENCE CHARACTERISTICS:

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- (2) INFORMATION FOR SEQ ID NO:430:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 61 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(x1) SEQUENCE DESCRIPTION: SEQ ID NO:429:
GGAGAGACA TGGGACAGG GCTATCGGA GGAATCACTT CCGCCAGAC
GACGACGGGG A 50 61
- (2) INFORMATION FOR SEQ ID NO:431:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 61 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(x1) SEQUENCE DESCRIPTION: SEQ ID NO:430:
GGAGAGACA TGGGACAGG GCTATCGGA GGAATCACTT CCGCCAGAC
GACGACGGGG A 50 61
- (2) INFORMATION FOR SEQ ID NO:432:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(x1) SEQUENCE DESCRIPTION: SEQ ID NO:431:
GGAGAGACA TGGGACAGG GCTATCGGA GGAATCACTT CCGCCAGAC
GACGACGGGG A 50 87
- (2) INFORMATION FOR SEQ ID NO:433:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 86 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(x1) SEQUENCE DESCRIPTION: SEQ ID NO:432:
ATCGCCCTGA TTAGCAGTAC TGAAGAGTA GAGGCGCAT CGCTCCGTAT
CAGGTCACT AGACTTGG CAAATCACC TGCAGGGG 50 86
- (2) INFORMATION FOR SEQ ID NO:434:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid

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- (C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:434:
CTACTACGA TGTACTAGC AGTCAGTGA CTTGAGTAA CCGATGCGTT 50
GGATATAG TAGCTACTC TCATGATTT CC 82
- (2) INFORMATION FOR SEQ ID NO:435:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 85 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:435:
CTACTACGA TGTACTAGC CTTCTAGAT GACTTCGAG GCATCGAAGC 60
TTACACTAT GGGTAGCTTA CTCACATTA TTCC 85
- (2) INFORMATION FOR SEQ ID NO:436:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 62 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:436:
GGAGAGACA TCGGGGGGCTT TATGCAATAC AGTCGCGATA NGCTAGCGGC 50
AGACGACGG GA 62
- (2) INFORMATION FOR SEQ ID NO:437:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 69 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:437:
GGAGAGACA TCGGGGGCTT GATGACGCT CGTAGGCGTA ANCCCGAAG 50
CCNCGACGA CGACGGGGG 69
- (2) INFORMATION FOR SEQ ID NO:438:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 61 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:438:
GGAGAGACA TCGGACCTG GTGGCTGTC TTATGTCGCC CTCATCAGAC 50
GACGACGGG A 61
- (2) INFORMATION FOR SEQ ID NO:439:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 60 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

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- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:439:
GGAGAGACA TCGGGGAGCC TGGGGTACAT CTCNAGCAA GCATCAGACG 50
ACGACGGGGA 60
- (2) INFORMATION FOR SEQ ID NO:440:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 61 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:440:
GGAGAGACA TCGGGGCTT GTACTGTTC TTATGTCCTC CACATCAGAC 50
GACGACGGG A 61
- (2) INFORMATION FOR SEQ ID NO:441:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 61 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:441:
GGAGAGACA TCGGGCTACT GTACTGCTTA TGTGTGTCCT CTCGTGAGAC 50
GACGACGGG A 61
- (2) INFORMATION FOR SEQ ID NO:442:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 61 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:442:
GGAGAGACA TCGGGGGGGA GTCAATCAC GCACCACTC CTCGTGAGAC 50
GACGACGGG A 61
- (2) INFORMATION FOR SEQ ID NO:443:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:443:
GGCGGGGCTA CGTACGGGG CTTGTGAAA CCCCCC 37
- (2) INFORMATION FOR SEQ ID NO:444:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 26 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-NH₂ cytosine
(ix) FEATURE:

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(D) OTHER INFORMATION: All U's are 2'-NH₂ uracil
FEATURE:

(A) NAME/KEY: C

(B) LOCATION: 26

(D) OTHER INFORMATION: The C at location 26 is
deoxycytidine

(X1) SEQUENCE DESCRIPTION: SEQ ID NO:444: 26
GGUGUGUGA AGACAGCGG UGGUUDC

(2) INFORMATION FOR SEQ ID NO:445:

(1) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 26 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(X1) SEQUENCE DESCRIPTION: SEQ ID NO:445: 26
GGTGTGTGA AGACAGCGG TGGTTC

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CLAIMS:

1. A method for identifying nucleic acid ligands to basic fibroblast growth factor (bFGF) comprising:
 - a) preparing a candidate mixture of nucleic acids;
 - b) contacting the candidate mixture with bFGF, wherein nucleic acid ligands having an increased affinity to bFGF may be partitioned from the remainder of the candidate mixture;
 - c) partitioning between members of said candidate mixture on the basis of affinity to bFGF; and
 - d) amplifying selected molecules of the candidate mixture with a relatively higher affinity for bFGF to yield a mixture of nucleic acids enriched for sequences with a relatively higher affinity to the protein, whereby nucleic acid ligands of bFGF may be identified.
2. The method of claim 1 further comprising
 - e) repeating steps b), c) and d).
3. The method of claim 1 wherein said candidate mixture of nucleic acids is comprised of single stranded nucleic acids.
4. The method of claim 3 wherein said candidate mixture of nucleic acids is comprised of RNA.
5. The method of claim 4 wherein said candidate mixture of nucleic acids is comprised of modified RNA.
6. The method of claim 5 wherein said candidate mixture of nucleic acids is comprised of RNA wherein all pyrimidines are 2'-deoxy-2'-NH₂ pyrimidines.
7. The method of claim 3 wherein said candidate

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mixture of nucleic acids is comprised of DNA.

8. A nucleic acid ligand to bPGF identified according to the method of claim 1.

9. The nucleic acid ligand of claim 8 comprising a single stranded nucleic acid.

10. The nucleic acid ligand of claim 8 comprised of RNA.

11. The nucleic acid ligand of claim 10 comprised of modified RNA.

12. The nucleic acid ligand of claim 11 comprised of RNA wherein all pyrimidines are 2'-deoxy-2'-NH₂ pyrimidines.

13. The nucleic acid ligand of claim 8 comprised of DNA.

14. The method of claim 2 further comprising f) identifying a nucleic acid ligand to bPGF from said mixture of nucleic acids enriched for sequences with a relatively higher affinity to bPGF.

15. The method of claim 14 further comprising f) chemically modifying said identified nucleic acid ligand.

16. A purified and isolated non-naturally occurring RNA ligand to bPGF.

17. The RNA ligand of claim 16 wherein the nucleic acid sequence of said ligand is selected from the group consisting of the nucleotide sequences set

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forth in Tables II, III, IV and VIII.

18. The RNA ligand of claim 16 wherein the nucleic acid sequence of said ligand is substantially homologous to and has substantially the same ability to bind bPGF as a ligand selected from the group consisting of the sequences set forth in Tables II, III, IV and VIII.

19. The RNA ligand of claim 16 wherein said ligand has substantially the same structure and substantially the same ability to bind bPGF as the sequences set forth in Tables II, III, IV, and VIII.

20. The RNA ligand of claim 16 wherein said ligand is an inhibitor of bPGF.

21. A purified and isolated non-naturally occurring DNA ligand to bPGF.

22. The DNA ligand of claim 21 wherein the nucleic acid sequence of said ligand is selected from the group consisting of the nucleotide sequences set forth in Tables XXI and XXII.

23. The DNA ligand of claim 21 wherein the nucleic acid sequence of said ligand is substantially homologous to and has substantially the same ability to bind bPGF as a ligand selected from the group consisting of the sequences set forth in Tables XXI and XXII.

24. The DNA ligand of claim 21 wherein said ligand has substantially the same structure and substantially the same ability to bind bPGF as the sequences set forth in Tables XXI and XXII.

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25. A method for treating bFGF-mediated pathological conditions comprising administering a pharmaceutically effective amount of a nucleic acid bFGF ligand.

26. The method of claim 25 wherein said nucleic acid bFGF ligand is identified according to the method of claim 1.

27. The method of claim 25 wherein said ligand is selected from one of the 2'-NH₂-modified ligands of Table VIII.

28. A method for identifying nucleic acid ligands to thrombin comprising:

a) preparing a candidate mixture of nucleic acids;

b) contacting the candidate mixture with thrombin, wherein nucleic acid ligands having an increased affinity to thrombin may be partitioned from the remainder of the candidate mixture;

c) partitioning between members of said candidate mixture on the basis of affinity to thrombin; and

d) amplifying selected molecules of the candidate mixture with a relatively higher affinity for thrombin to yield a mixture of nucleic acids enriched for sequences with a relatively higher affinity to the protein, whereby nucleic acid ligands of thrombin may be identified.

29. The method of claim 28 further comprising

e) repeating steps b), c) and d).

30. The method of claim 28 wherein said candidate mixture of nucleic acids is comprised of single stranded nucleic acids.

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31. The method of claim 30 wherein said candidate mixture of nucleic acids is comprised of RNA.

32. The method of claim 30 wherein said candidate mixture of nucleic acids is comprised of DNA.

33. A RNA nucleic acid ligand to thrombin identified according to the method of claim 28.

34. A DNA nucleic acid ligand to thrombin identified according to the method of claim 28.

35. The nucleic acid ligand of claim 32 being a single stranded nucleic acid.

36. A purified and isolated non-naturally occurring RNA ligand to thrombin wherein the nucleic acid sequence of said ligand is selected from the group consisting of the sequences set forth in Table XII.

37. The RNA ligand of claim 36 wherein said ligand is substantially homologous to and has substantially the same ability to bind thrombin as a ligand selected from the group consisting of the sequences set forth in Table XII.

38. The RNA ligand of claim 36 wherein said ligand has substantially the same structure and substantially the same ability to bind thrombin as the sequences set forth in Table XII.

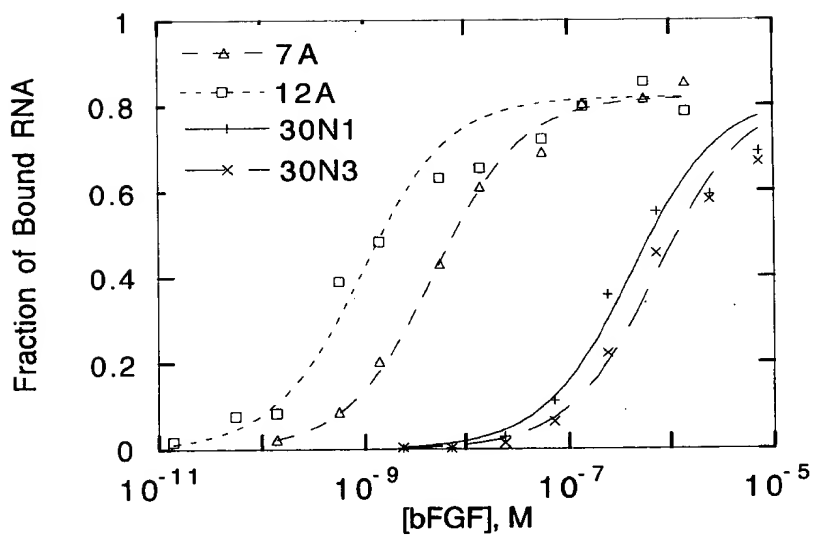
39. A purified and isolated non-naturally occurring DNA ligand to thrombin wherein the nucleic acid sequence of said ligand is selected from the group consisting of the sequences set forth in Tables XV and XVI.

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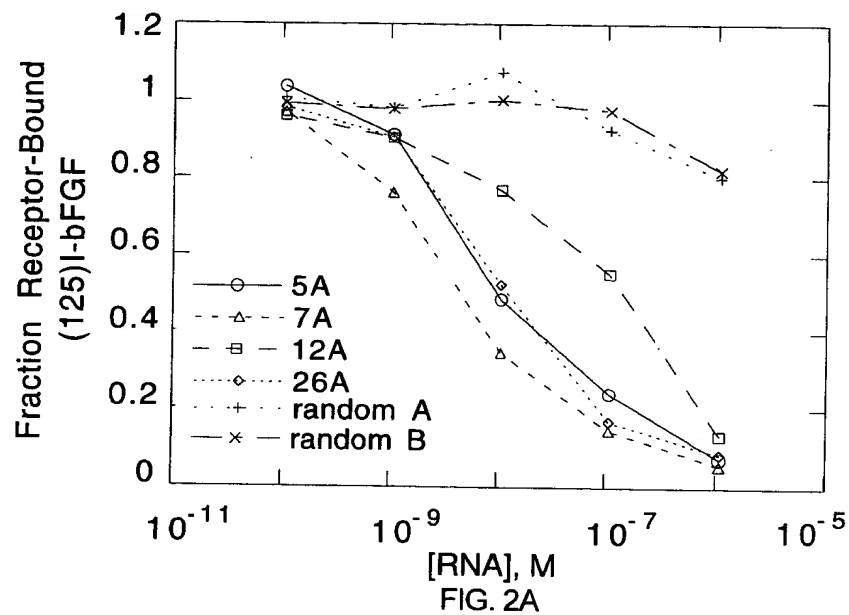
40. The DNA ligand of claim 39 wherein said ligand is substantially homologous to and has substantially the same ability to bind thrombin as a ligand selected from the group consisting of the sequences set forth in Table XV and XVI.

41. The DNA ligand of claim 39 wherein said ligand has substantially the same structure and substantially the same ability to bind thrombin as the sequences set forth in Table XV and XVI.

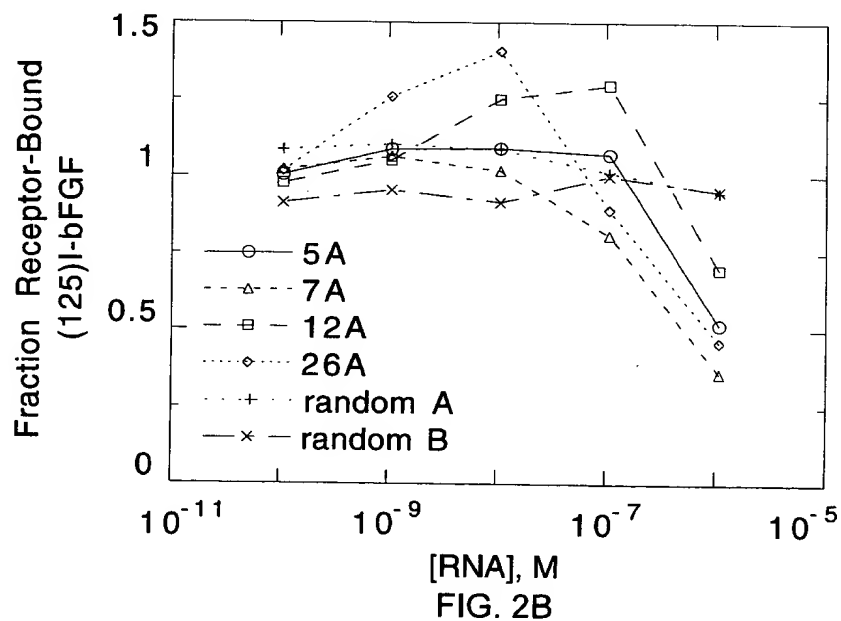
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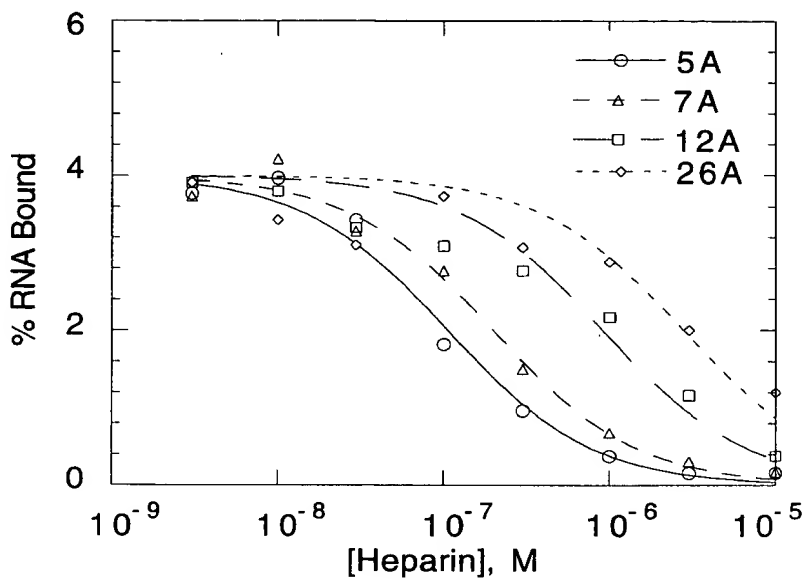


FIG. 3

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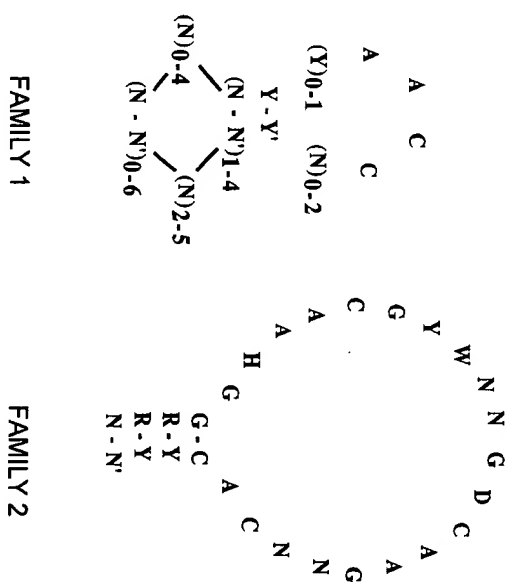


FIG. 4

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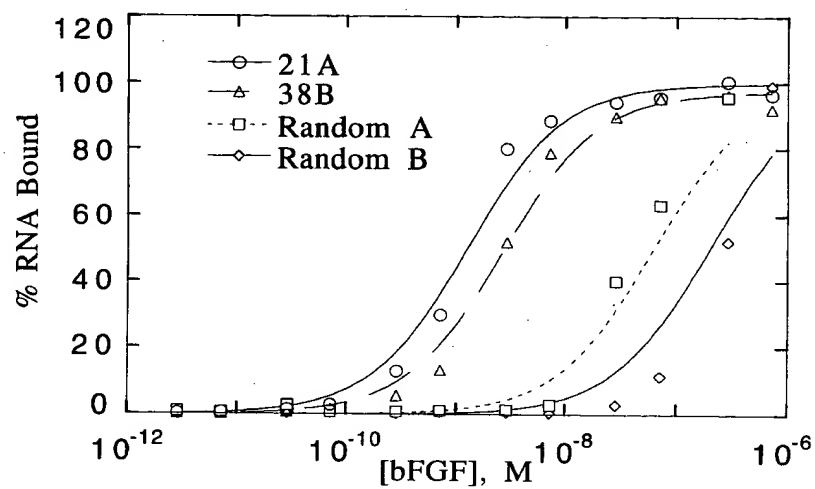


FIG. 5

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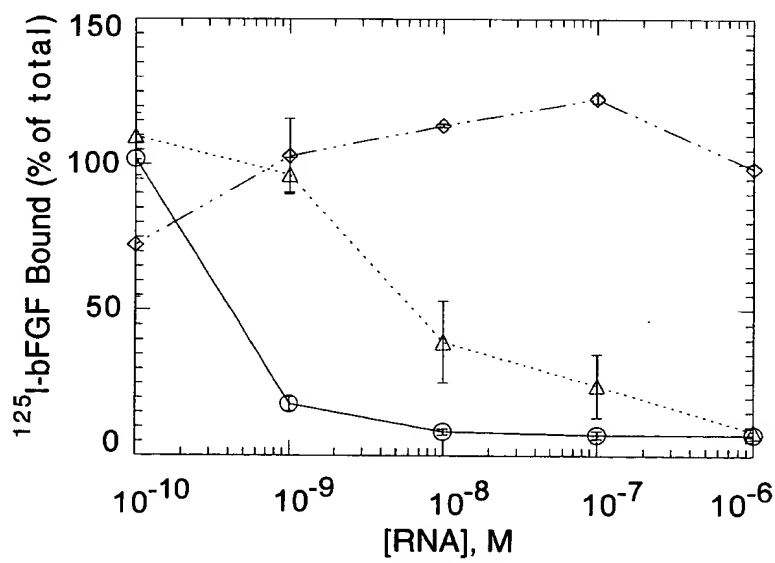


FIG. 6A

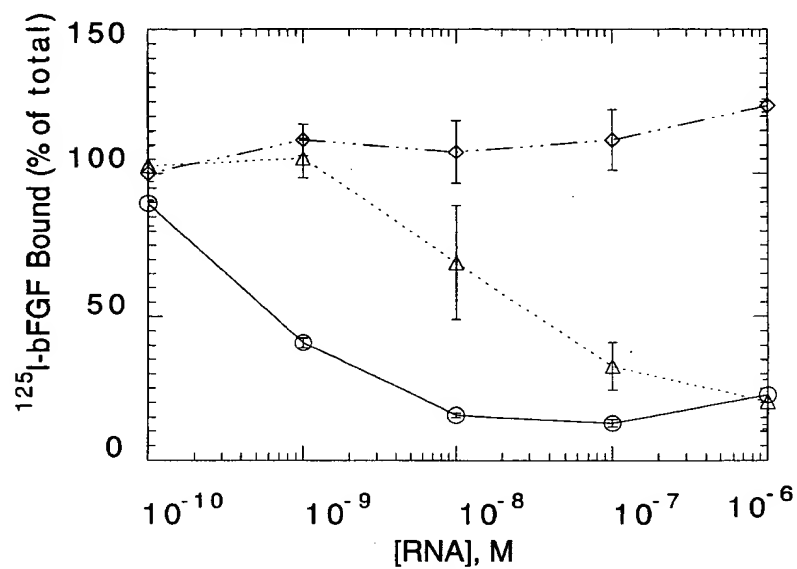
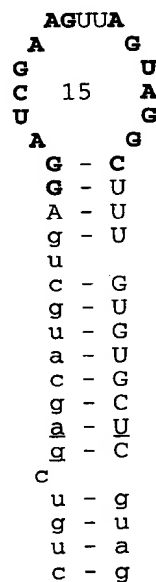


FIG. 6B

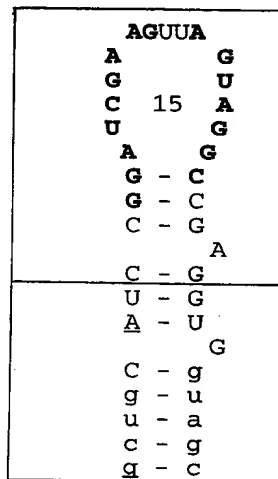
CLONE 6



acgu = fixed region
 ACGU = random region
ACGU = conserved region
 — = boundaries

gggagaucg cuaaacagcuuugucgacggg
 SEQ ID NO:211
 FIG. 7

CLONE 16



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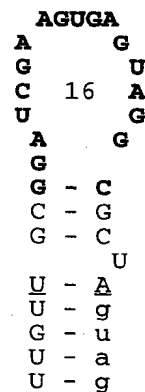
gggagaugccugucgagcau uaaacagcuuugucgacggg

SEQ ID NO:212
FIG. 7 (CONT'D)

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CLONE 18



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acgu = fixed region
ACGU = random region
ACGU = conserved region
— = boundaries

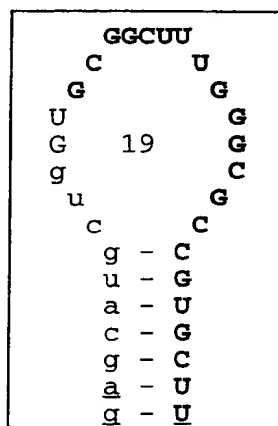
ggg|agaugccugucgagcaugcugA cuaaagagcuuugucgacggg

SEQ ID NO:213
FIG. 7 (CONT'D)

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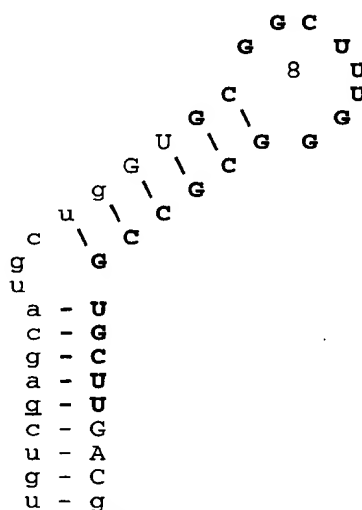
gggagauGCC

uagcuaaagagcuuugucgacggg

PCT/US95/01458

SEQ ID NO:214
FIG. 7 (CONT'D)

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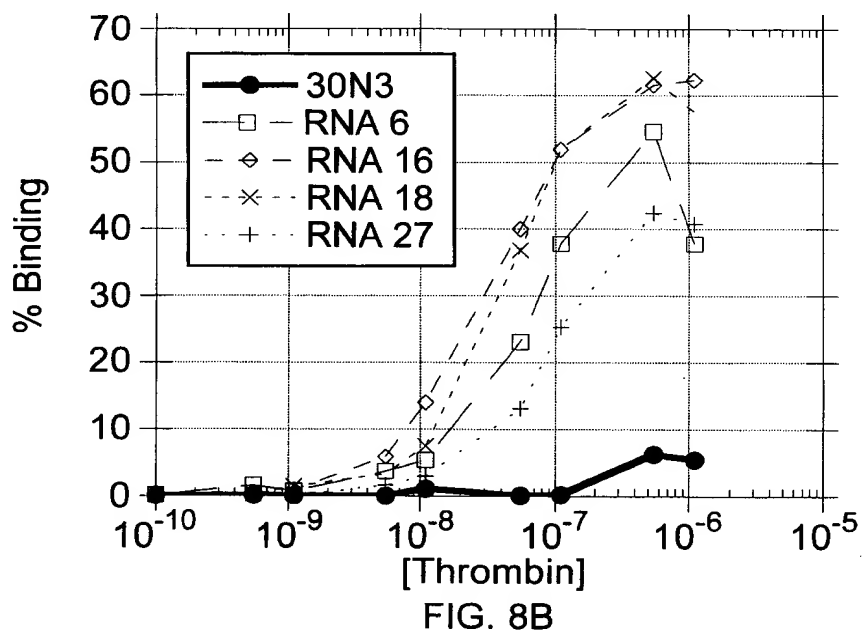
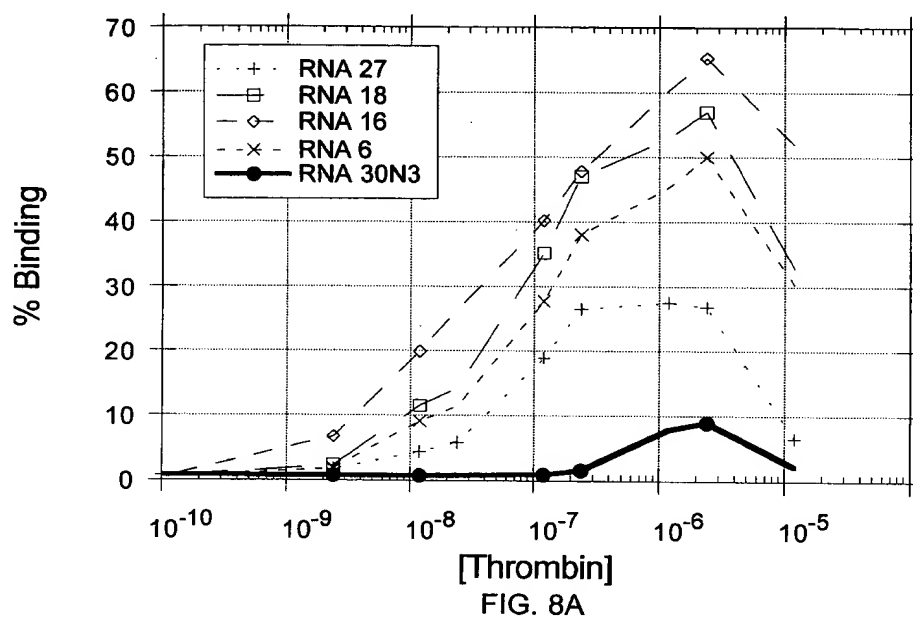
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gggagauGCC

uagcuaaagagcuuugucgacggg

PCT/US95/01458

SEQ ID NO:215
FIG. 7 (CONT'D)



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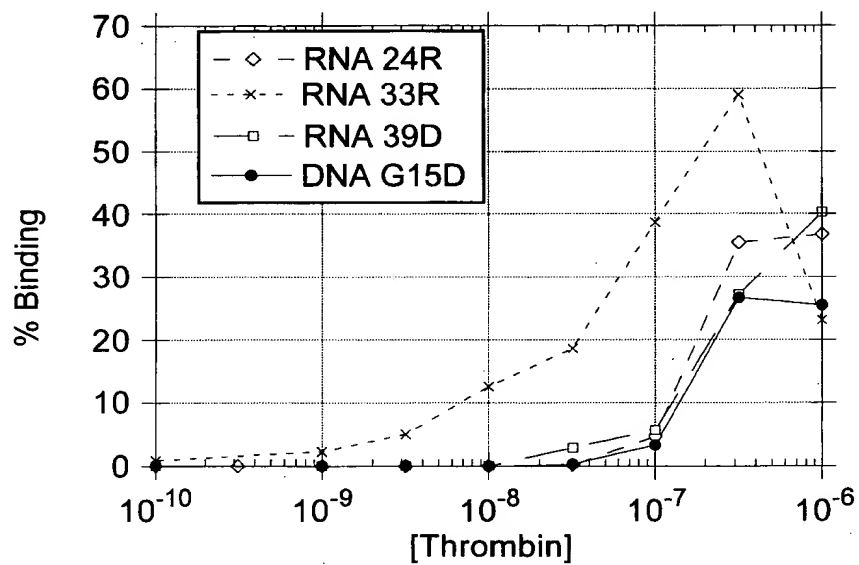


FIG. 8C

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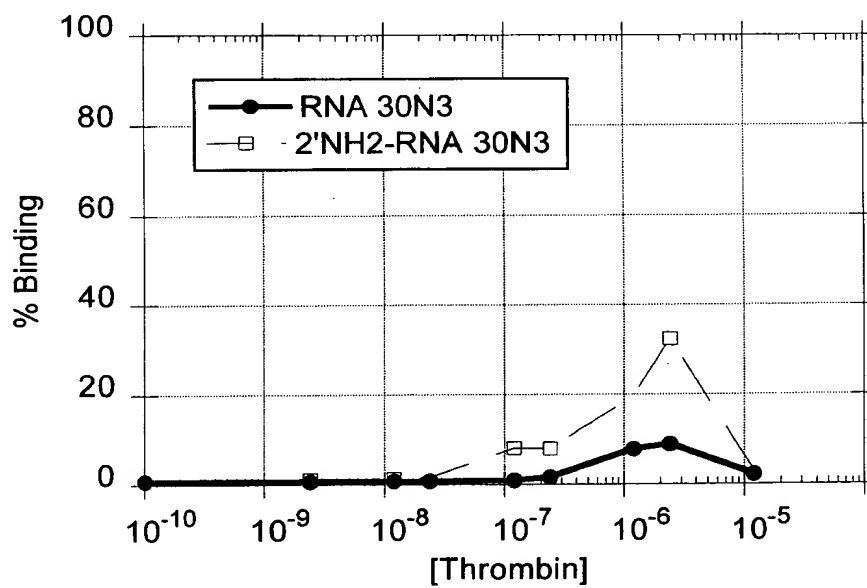


FIG. 9A

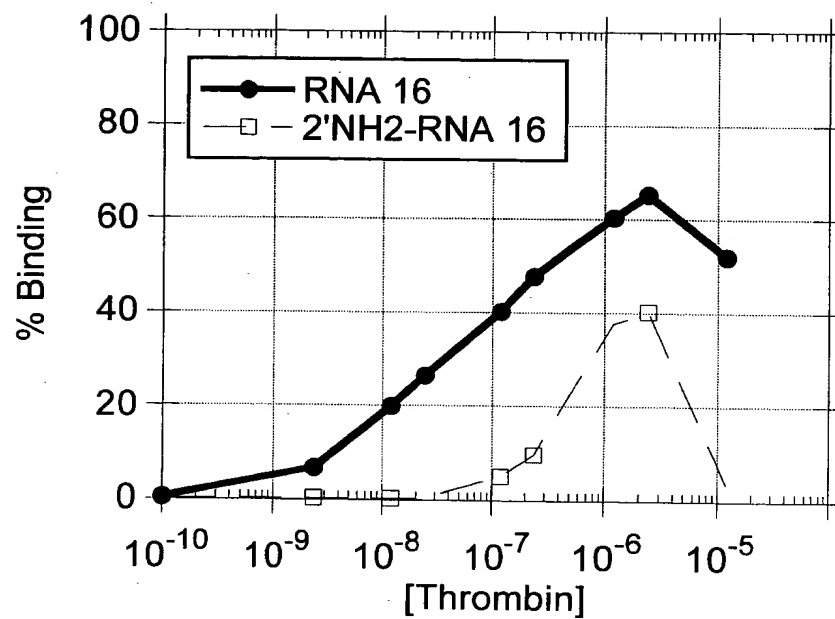


FIG. 9B

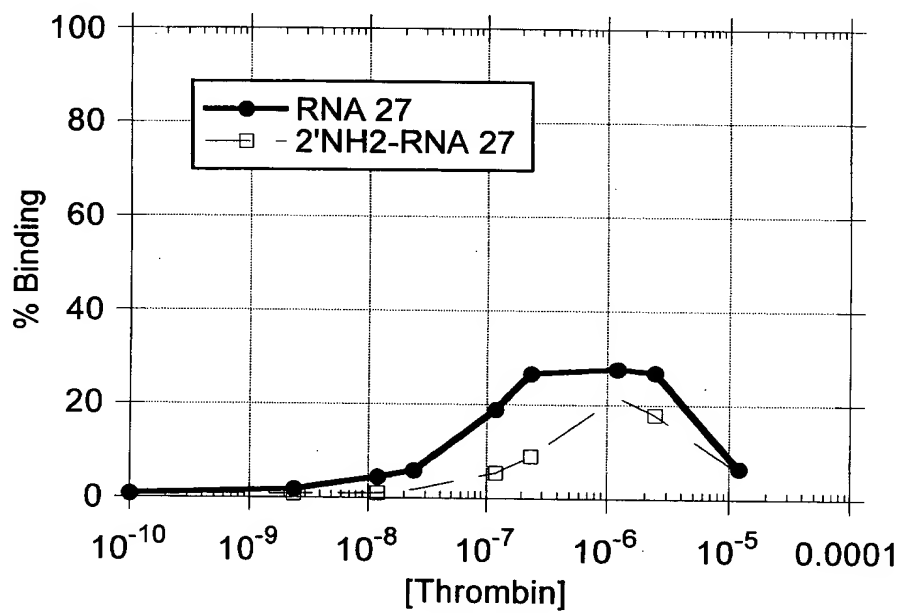
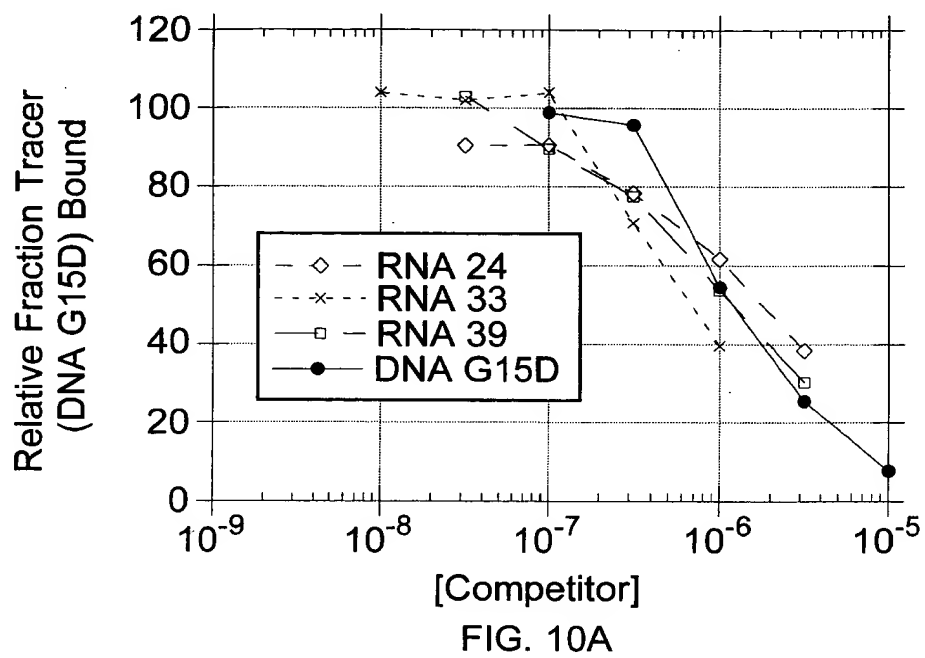


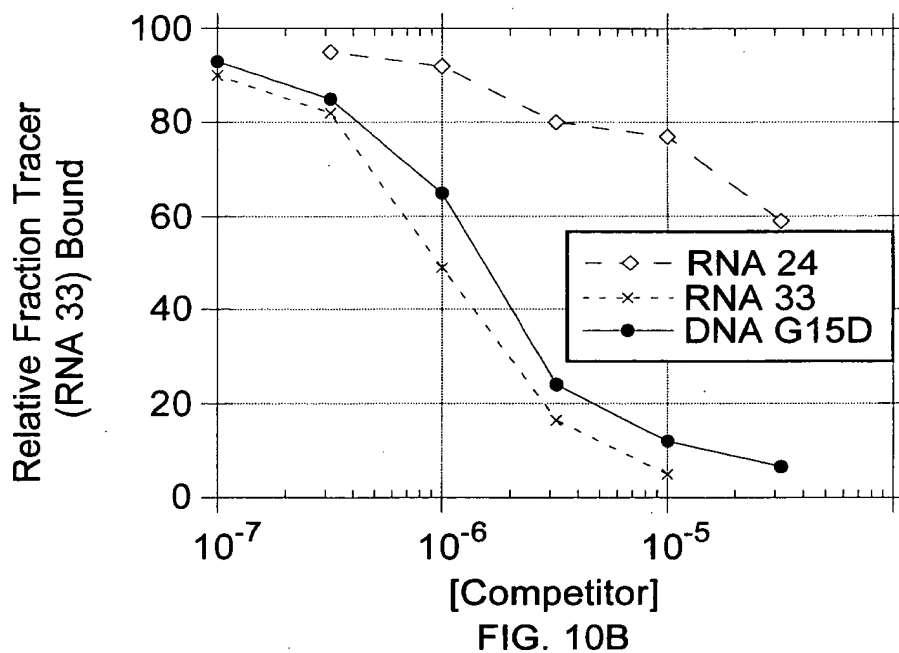
FIG. 9C



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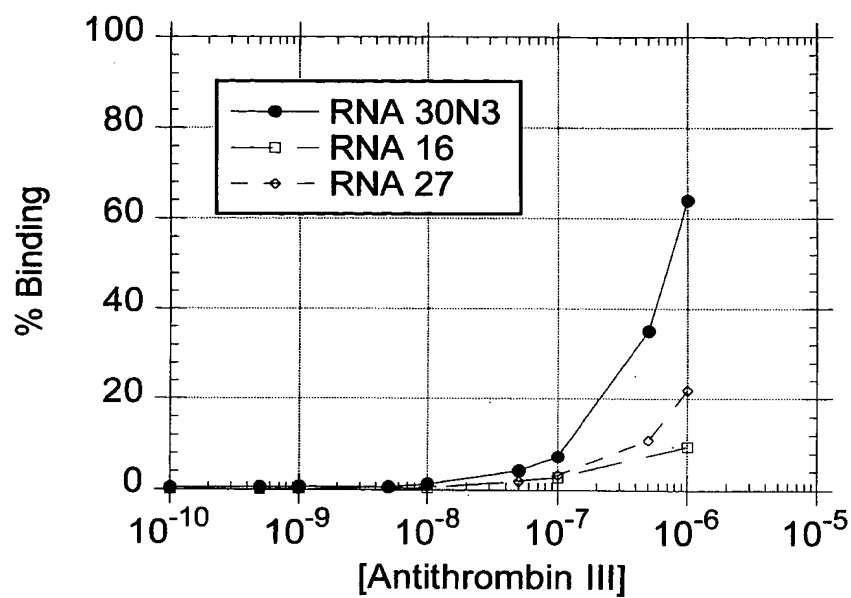


FIG. 11A

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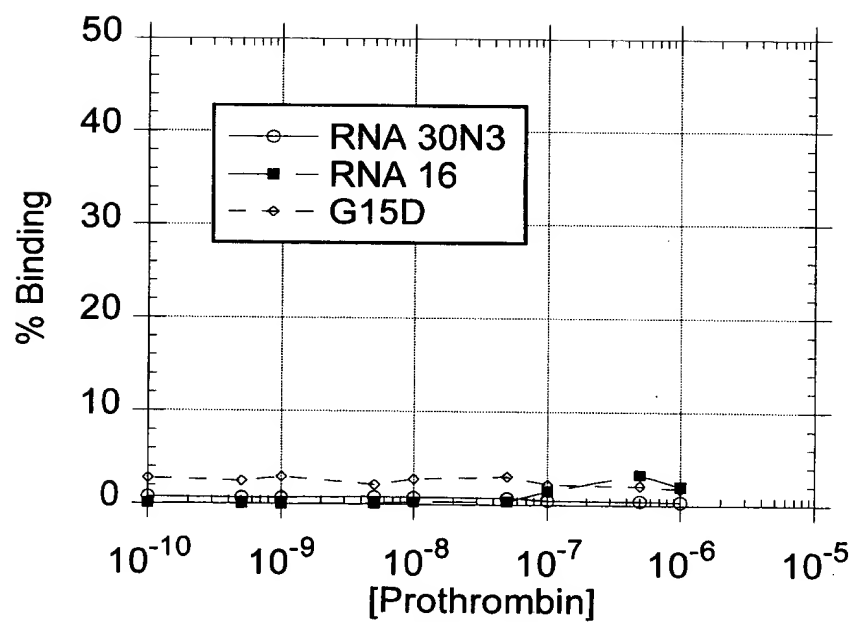


FIG. 11B

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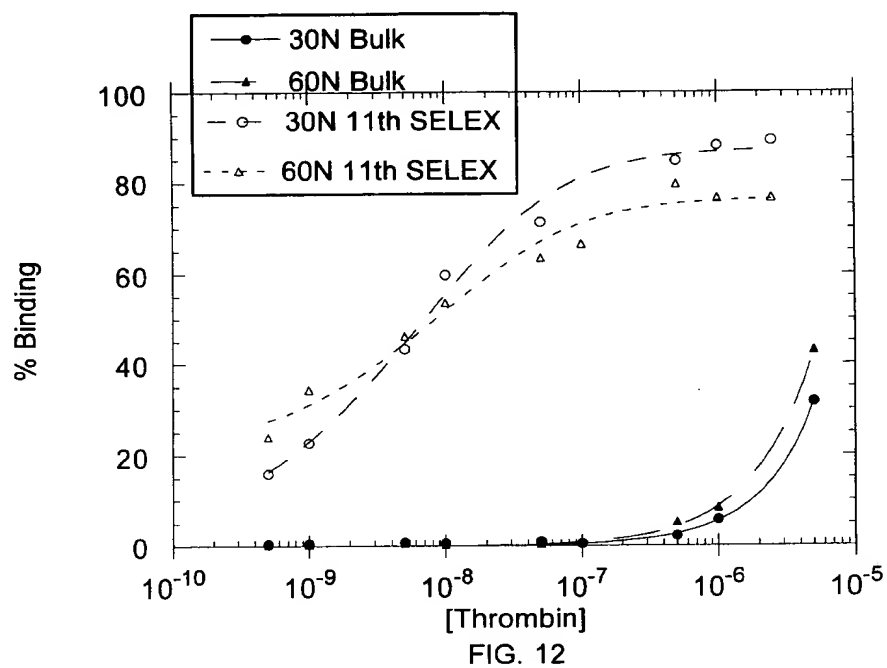


FIG. 12

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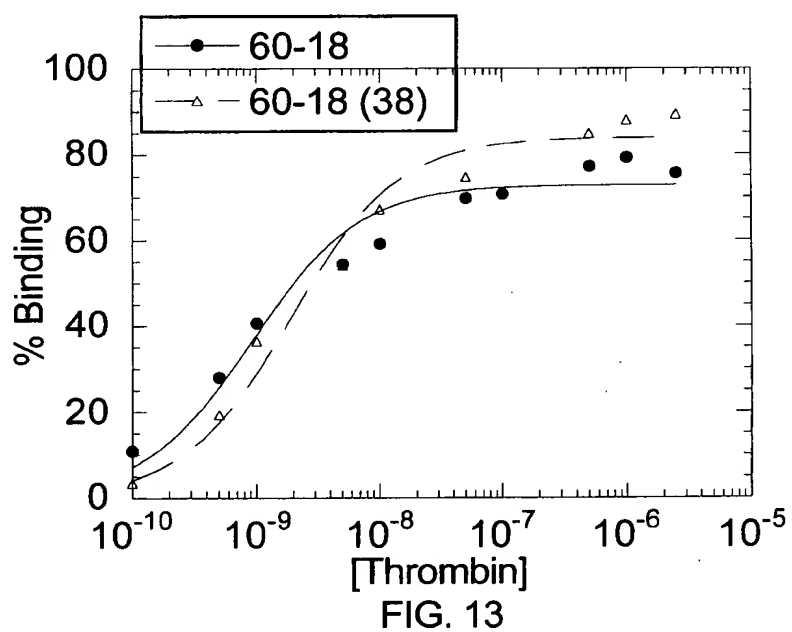


FIG. 13

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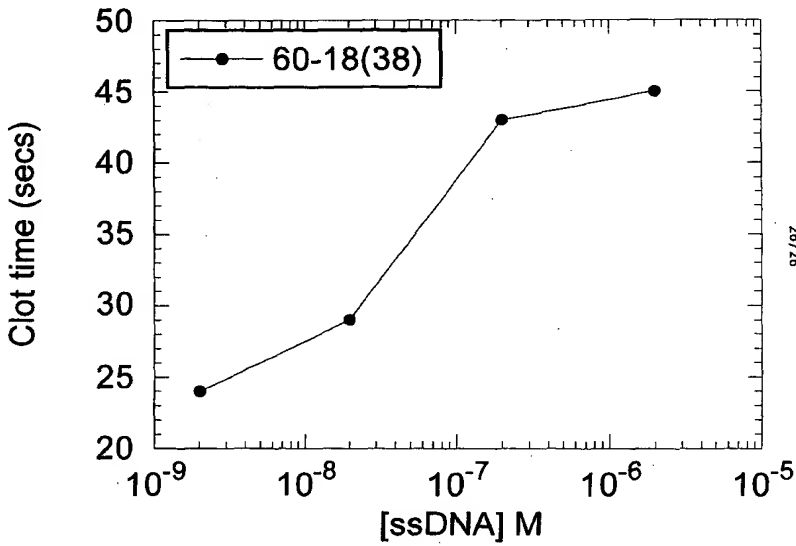


FIG. 14

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US95/01458

A. CLASSIFICATION OF SUBJECT MATTER

IPC(9) : C07H 21/02, 21/04; C12P 19/34; C12Q 1/68
US CL : 4356, 91.2; 536/22.1

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 4356, 91.2; 536/22.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
APS, DIALOG: nucleic, binding, ligand, growth factor, thrombin

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|-----------|---|--|
| X | Proceedings of the National Academy of Sciences, USA, Vol. 90, issued December 1993, Jellinek, D. et al., "High-Affinity RNA Ligands to Basic Fibroblast Growth Factor Inhibit Receptor Binding", pages 11227-11231, see entire document. | 1-5, 8-10, 14, 16-20, 26 6, 7, 11-13, 15, 21-25 |
| Y | Proceedings of the National Academy of Science, USA, Vol. 88, issued April 1991, Eriksson, A. et al., "Three-Dimensional Structure of Human Basic Fibroblast Growth Factor", pages 3441-3445, see entire document | 1-27 |

* Further documents are listed in the continuation of Box C. ☐ See patent family status.

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* Documents which may have priority claims or which are cited to establish the publication date of another citation or other special interest (in particular)

* Documents relating to an oral disclosure, use, exhibition or other

* Documents published prior to the international filing date but later than the priority date claimed

Date of the actual completion of the international search

10 MAY 1995

Date of mailing of the international search report

22 MAY 1995

Name and mailing address of the ISA/US

Communicator of Patents and Trademarks

Washington, D.C. 20531

Filing No. (70) 305-3220

Telephone No. (70) 308-0196

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Authorized officer: *Dunbar*
STEPHANIE W. ZITOMER, Ph.D.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US95/01458

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|-----------|--|---|
| X | Nature, Vol. 335, issued 06 February 1992, Bock, L. et al., "Selection of Single-Stranded DNA Molecules That Bind and Inhibit Human Thrombin", pages 564-566, see entire document | 28-30, 32, 34, 35, 39-41 31, 33, 36-38, 37 |
| Y | Science, Vol. 249, issued 03 August 1990, Tuerk, C. et al., "Systematic Evolution of Ligands by Exponential Enrichment: RNA Ligands to Bacteriophage T4 DNA Polymerase", pages 505- 510, see entire document | 1-41 |
| Y | Proceedings of the National Academy of Science, USA, Vol. 88, issued April 1991, Zhang, J. et al., "Three-Dimensional Structure of Human Basic Fibroblast Growth Factor, a Structural Homolog of Interleukin 16", pages 3446-3450, see entire document. | 1-27 |

